

Exhibit 3

EXPERT REPORT, ANNA LEMBKE, M.D.

March 25, 2019

MDL No. 2804

Relating to Case Nos. 17-OP-45004 and 18-OP-45090

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Appendix I: Misleading Promotional Messages

IA: Purdue
IB: Mallinckrodt
IC: Janssen
ID: Endo
IE: Allergan

Appendix II: Summary of Documents from the University of Wisconsin Pain & Policy Study Group (PPSG)

Exhibit A: Curriculum Vitae of Anna Lembke, M.D.

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A. Background and Qualification

1. I am an Associate Professor, Chief of the Addiction Medicine Dual Diagnosis Clinic, Medical Director of Addiction Medicine, and Program Director of the Addiction Medicine Fellowship, in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Since 2016, I also hold a Courtesy Appointment in the Stanford University Department of Anesthesiology and Pain Medicine. I began my faculty career at Stanford in 2003. A true copy of my current CV is attached to this Report as Exhibit A.

2. I received my undergraduate degree in Humanities from Yale University in 1989, and my medical degree from Stanford University in 1995, where I also completed a partial residency in Pathology (1997) and a full residency in Psychiatry (2000), as well as a Fellowship in Mood Disorders, Department of Psychiatry and Behavioral Sciences (2002).

3. I have been licensed to practice medicine in the State of California from 1995 to the present. I received the DEA-X waiver to prescribe buprenorphine products in 2013. I am a diplomate of the American Board of Psychiatry and Neurology (2003; recertified, 2013), and a diplomate of the American Board of Addiction Medicine (2013).

4. From 2001 to the present, I have taught medical students, residents, and fellows at Stanford University School of Medicine, on a diversity of topics related to psychiatry, addiction, and pain. For example, from 2004 to the present, I have given annual lectures on addiction medicine within the Practice of Medicine (POM) series for Stanford medical students, including topics such as the neurobiology of addiction, how doctors should intervene when they detect substance use problems, and how to have difficult conversations with patients on the topic of substance use, misuse, overuse, and addiction.

5. I received the Stanford Award for Excellence in Academic Teaching, Department of Psychiatry, in 2014, and again in 2018.

6. As a full time faculty at the Stanford University School of Medicine, I regularly treat patients with addiction to opioids and other substances. For the last 15 years, my clinical practice has included a significant proportion of patients taking prescription opioids for pain relief, for whom such drugs have resulted in misuse, dependence, and addiction. As an integral part of my practice, I work with these patients to develop treatment plans that will address their pain while making appropriate efforts to reduce (taper) or eliminate use of opioids, and/or treat their opioid addiction. Such plans can include non-opioid medications for pain, as well as alternative, non-pharmaceutical modalities, and counseling, with a dual focus on treating the underlying painful condition and the substance use disorder. I also see patients within the Stanford Pain Clinic, where I provide expert consultation in pain and addiction.

7. In 2015, I received the Stanford Chairman's Award for Clinical Innovation for developing inpatient and outpatient clinical services dedicated to helping people with substance use problems.

8. In January 2015 I was appointed by Governor Jerry Brown to the Research Advisory Panel of California. I served on the Panel until 2017. I, along with the other Panel members, was tasked with assessing the safety of clinical trials to be conducted in the state of

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California using controlled substances, such as opioids. In this capacity, I applied my knowledge and experience to the review of study designs and protocols, and I made recommendations for procedures to protect patients in these trials, including, in particular, protection from potential harmful effects of opioids.

9. Since 2015 I have served on the Board of the California Society of Addiction Medicine (CSAM). I have been a member of CSAM, and the American Society of Addiction Medicine (ASAM), since 2011.

10. In 2016 I chaired the Planning Committee for the California Society of Addiction Medicine (CSAM) Annual Addiction Medicine Conference.

11. In 2016, I became president of the Addiction Medicine Fellowship Directors Association (AMFDA).

12. In 2016 I led a program funded by the Stanford Center for Continuing Medical Education (SCCME), titled, “Tapering Patients off of Chronic Opioid Therapy.”¹

13. Since 2016, I have chaired the Addiction Medicine Task Force, Stanford University School of Medicine. The goal of the Task Force is to re-evaluate and re-create the medical school curriculum on addiction and safe prescribing of addictive substances. I have served as MedScholar Advisor on the topic of *Developing the Addiction Curriculum at Stanford*, Stanford University School of Medicine.

14. I am the author of a book on the prescription drug epidemic: “Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop” (Johns Hopkins University Press, October 2016).²

15. I have published over 50 peer-reviewed articles, chapters, and commentaries, which have appeared in the New England Journal of Medicine, Journal of the American Medical Association, Pain Medicine, Journal of General Internal Medicine, Addiction, and other peer reviewed journals. Many of these publications address the diagnosis and treatment of addiction, as well as the treatment of pain. I have also published articles on the importance of teaching addiction medicine in medical school, residency, and fellowship, (as discussed in this report).

16. In 2016 I co-authored a peer-reviewed article, “Weighing the Risks and Benefits of Chronic Opioid Therapy,” American Family Physician 2016; 93:982-990, which addressed issues of opioid misuse and addiction, risk assessment and mitigation, patient education, tapering to reduce or end opioid exposure, tolerance, dependence, and risks of overdose.³ American Family Physician is among the most read family physician peer reviewed journals. The readership includes 32,000 medical students and over 3,700 nurse practitioner and physician assistant subscribers.

¹ <https://med.stanford.edu/cme/courses/online/opioid-taper.html>

² Lembke A. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop*. 1st ed. Johns Hopkins University Press; 2016

³ Lembke A, Humphreys K, Newmark J. Weighing the risks and benefits of chronic opioid therapy. *Am Fam Physician*. 2016; in press

17. In 2016 I co-authored a Research Letter, *JAMA Intern Medicine* 2016;176(2):259-261, which examined Medicare data on opioid drug prescription patterns. Our analysis concluded that opioid prescribing is “a widespread practice relatively indifferent to individual physicians, specialty or region. High-volume prescribers are not alone responsible for the high national volume of opioid prescriptions. Efforts to curtail national opioid overprescribing must address a broad swath of prescribers to be effective.”⁴(pp. 260-261) This article has been cited 71 times in the 3 years since its publication, and has helped to counter the notion that the epidemic of opioid drug misuse and addiction is primarily attributable to a small group of “pill mill” doctors.

18. In 2016 I co-authored a Research Letter, *JAMA Psychiatry*, 2016;73(9), on the high exposure to opioids among Medicare patients, the growing incidence of opioid use disorder in this population, and the lack of buprenorphine prescribers in this population, noting the gap between the need for treatment, and access to that treatment.⁵

19. In 2018 I co-authored two articles in peer-reviewed pain journals on pain management of patients with chronic pain and opioid use disorder.^{6,7}

20. I have testified before the United States House of Representatives on the opioid epidemic and possible means to mitigate harms caused by that epidemic, and I have presented at numerous conferences before governmental, professional, academic and lay audiences on related topics.

21. In forming the opinions expressed in this Report, I have relied on my medical training, more than twenty years of clinical experience, and my own research on opioid prescribing. My research began circa 2001 and has been multimodal. I have done qualitative interviews with patients, providers, and others in the health care field on questions related to opioid prescribing. I have followed and analyzed the medical literature using PubMed and other academic search engines, along with different combinations of key words such as “pain, opioids, treatment, randomized clinical trials, open label trials, effectiveness, adverse effects, prescribing, addiction, dependence, overdose, etc. ...” I have compiled statistics published by the CDC and other government agencies. I have, in collaboration with colleagues, analyzed opioid prescribing databases such as Medicare Part D.^{8,9} As a regular and ongoing part of my practice, I conduct literature searches of research on the subjects of addiction and pain treatment, which is essential

⁴ Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of opioids by different types of medicare prescribers. *JAMA Intern Med.* December 2015;1-3. <http://dx.doi.org/10.1001/jamainternmed.2015.6662>, at pp. 260-261.

⁵ Lembke A, Chen JH. Use of opioid agonist therapy for medicare patients in 2013. *JAMA Psychiatry.* 2016;73(9). doi:10.1001/jamapsychiatry.2016.1390

⁶ Harrison TK, Kornfeld H, Aggarwal AK, Lembke A. Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiol Clin.* 2018;36(3):345-359. doi:10.1016/j.anclin.2018.04.002

⁷ Lembke A, Ottestad E, Schmiesing C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. *Pain Med.* 2018;(February):1-4. doi:10.1093/pm/pny019

⁸ Chen et.al, “Distribution of Opioids,” fn. 4, above, at p. 259

⁹ Lembke, *et al.*, “Use of Opioid Agonist Therapy,” fn. 5, above, at p. 990

to my work with my patients. Indeed, given the large and increasing role of opioid drugs in addiction, the fields of addiction and pain medicine are inevitably intertwined, such that it is essential to my practice to remain aware of the state of scientific inquiry in both fields. Specifically for this Report, I have considered the materials listed on Exhibit B, attached. I hold the opinions stated in this Report to a reasonable degree of scientific certainty.

22. A statement of my testimony within the last 4 years is attached as Exhibit C and a statement of my compensation rate for consulting work is attached as Exhibit D.

B. Opinions

For the reasons set forth in detail in this Report, I hold the following opinions:

1. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting widespread access to prescription opioids has inevitably resulted in an epidemic of opioid addiction.

2. Opioid prescribing began to increase in the 1980's, and became prolific in the 1990's and the early part of the 21st century, creating more access to opioids across the U.S. population, and representing a radical paradigm shift in the treatment of pain. Prior to 1980, doctors prescribed opioid pain relievers sparingly, out of appropriate concern that their patients would get addicted, and then only for short term use in cases of severe injury, surgery, or at the very end of life.

3. The Pharmaceutical Opioid Industry increased sales of prescription opioids, by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like The Joint Commission, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread opioid prescribing.

4. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including the following:

- a. overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best evidence available shows that there is little or no improvement in pain or function for most patients on long-term opioid therapy. Patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids.

Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment. As a part of the overstatement of benefits, the Pharmaceutical Opioid Industry promoted the concept of “undertreatment of chronic pain” on a massive scale. The number of people who suffer from chronic pain varies substantially, depending on how “chronic pain” is defined. Regardless of the definition or true number, the fact remains that there is insufficient evidence that long-term opioid therapy effectively treats chronic pain.

- b. making inaccurate understatements of the risks of addiction to opioids. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain. There is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, “rare,” or “less than 1%.” In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 29%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction. So-called “abuse-deterrent formulations” do not lower the risk of addiction among patients taking them as prescribed.
- c. making inaccurate claims as to the levels to which doses can be safely increased. With increasing dosage and duration of opioids, the risk of addiction goes up, as do the risks of many other adverse health consequences, including tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, severe constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, accidental overdose, and death. There is an undeniable link between opioids and suicides. Opioids are associated with more adverse medical outcomes and more mortality than non-opioid analgesics (NSAIDs).
- d. mischaracterizing addictive behavior as “pseudoaddiction” and tolerance as “breakthrough pain.” There is no such thing as “pseudoaddiction,” and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.
- e. characterizing opioid dependence as a benign state that is easily reversible. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Once established, opioid dependence represents a complex, debilitating, and

sometime irreversible clinical problem. In most cases, these patients require a protracted, medically supervised taper to lower their doses. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.

- f. inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.

5. In sum, the Pharmaceutical Opioid Industry made misleading marketing claims to promote the above misconceptions, in the absence of reliable scientific evidence. Taken together, these misconceptions were a primary driver of the massive increase in the sale of opioids and the resulting epidemic of dependence and addiction, as detailed in this Report. Further, the actions of the Pharmaceutical Opioid Industry significantly influenced doctors and others who made decisions that increased the population's exposure to prescription opioids. Other developed countries with similar populations that experience chronic pain, but which have not had the same aggressive marketing as in the U.S., have not experienced any comparable degrees of prescription opioid overuse, mortality, and morbidity.

6. The increase in opioid sales resulted in a prescription opioid epidemic in the United States. "Epidemic," defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990's and continuing to the present day. This epidemic is first and foremost a prescription opioid epidemic, with prescription opioids accounting for a higher number of cumulative deaths to date (1999-2017) than heroin and illicit fentanyl combined.

7. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). There is a clear link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids. The likelihood of heroin addiction is 40 times greater in those who have previously misused or been addicted to prescription opioids.

8. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to be exposed and become addicted, including individuals who turned from prescription opioids to illicit sources of opioids such as heroin (The Gateway Effect).

9. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to become dependent on

opioids (independent of addiction), and suffer significant morbidity and mortality as a result (The Dependence Effect).

10. The increased sales of prescription opioids harmed communities by causing a dramatic increase in the widespread availability of opioids, including to persons for whom opioids had not been prescribed (The Tsunami Effect). Medical prescriptions are the primary conduit for prescription opioid misuse. Less than 10% of Americans misusing prescription opioids got them from a “street dealer.”

11. Others bear some lesser responsibility for the events that have transpired since 1995 with respect to the overuse of prescription opioids. However, none of those events would have occurred, nor would they have been possible, but for the aggressive marketing by the Pharmaceutical Opioid Industry and the myths of significant benefits versus low risk that they promoted, as outlined above and detailed in the body of this Report.

12. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

C. Detailed Statement of Opinions

1. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. As stated by the CDC, “Anyone who takes prescription opioids can become addicted to them.”¹⁰ Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. Prescription opioids are as addictive as heroin, and the Defendants’ conduct in promoting widespread access to prescription opioids has inevitably resulted in an epidemic of opioid addiction.

- a. Addiction is the continued use of a substance despite harm to self and others and/or a desire to quit or cut back. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)¹¹ uses the term “substance use disorder” to denote addiction. I use the terms “opioid addiction” and “opioid use disorder” interchangeably here.
- b. DSM-5 denotes 11 different criteria to diagnose an opioid use disorder (OUD) (p. 541). A short-hand way to remember these criteria is the “four

¹⁰ <https://www.cdc.gov/drugoverdose/opioids/prescribed.html>.

¹¹ *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association (DSM-5); 2013

C's": Control, Compulsion, Craving, and continued use despite Consequences.

- i. Control refers to out-of-control use, for example using more than intended, or an inability to cut back use when necessary.
 - ii. Compulsion refers to mental preoccupation with using against a conscious desire to abstain.
 - iii. Craving refers to physiologic and/or mental states of wanting.
 - iv. Consequences refers to the social, legal, economic, interpersonal, and other problems that arise as a result of use, yet which still do not deter use.
- c. The physiological phenomena of tolerance and withdrawal are included in the DSM-5 criteria, but they are not required in order to make the diagnosis of opioid use disorder/addiction. In other words, tolerance, dependence, and withdrawal are recognized as separate physiologic phenomena often seen in addiction, but not definitional for addiction. The DSM-5 also recognizes that addiction is a spectrum disorder, divided into mild, moderate, and severe, based on the number of criteria met.¹²
- d. The American Society of Addiction Medicine (ASAM) has defined addiction as follows: "Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death."¹³ This ASAM definition of addiction is consistent with but not identical to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The ASAM definition does not single out any specific substance, highlighting the idea that all addictive drugs work on the same common brain pathway.

¹² DSM-5, fn. 11, above, pp. 541-542.

¹³ American Society of Addiction Medicine (ASAM) Definition of Addiction.
<https://www.asam.org/resources/definition-of-addiction>; accessed June 20, 2018, at p. 1.

- e. From a neuroscience perspective, addiction is a disorder of the brain's reward circuitry.¹⁴ Opioids, in addition to binding the mu-pain receptors, also cause the release of the neurotransmitter dopamine. In order to accommodate the high amount of dopamine released, the brain adapts by downregulating its own endogenous dopamine and its own endogenous dopamine receptors. This process is called neuroadaptation, and the result is a dopamine deficit state, wherein the threshold for experiencing pleasure goes up, and the threshold for experiencing pain goes down. Addicted individuals then need the substance not to feel good, but to escape the pain of withdrawal.
- f. In severe forms of addiction, individuals commit all available resources to obtaining more of the substance, even forgoing natural rewards like food, finding a mate, or raising children.¹⁵ By hijacking the brain's reward and motivational centers, addiction leads to compulsive, self-destructive consumption that overcomes the limits of voluntary choice.
- g. Because addiction affects the same neural pathways evolved over millions of years to encourage humans to seek out pleasure and avoid pain, everyone is vulnerable to the disease of addiction. Or as Nora Volkow, Director of the National Institute on Drug Abuse, and Thomas McLellan, former Deputy Director of the Office of National Drug Control Policy, wrote in their review "Opioid Abuse in Chronic Pain" in the *New England Journal of Medicine* (2016), "no patient is immune to addiction."¹⁶ Without activation by consumption of the drug, the disease of addiction does not exist. This is supported by studies that have identified a dopamine receptor deficit state among those exposed to addictive drugs, compared to healthy subjects who have not been exposed.¹⁷ Exposure to/consumption of the addictive substance is a necessary criterion for the development of addiction to that substance.

2. Opioid prescribing began to increase in the 1980's, and became prolific in the 1990's and the early part of the 21st century, creating more access to opioids across the U.S. population, and representing a radical paradigm shift in the treatment of pain. Prior to 1980, doctors prescribed opioid pain relievers sparingly, out of appropriate concern that their patients would get addicted, and then only for short term use in cases of severe injury, surgery, or at the very end of life.

¹⁴ Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35:217-238. doi:10.1038/npp.2010.4

¹⁵ Schultz W. Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. *Neuron*. 2011;69(4):603-617. doi:10.1016/j.neuron.2011.02.014

¹⁶ Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain - Misconceptions and Mitigation Strategies. *N Engl J Med*. 2016;374(13):1253-1263. doi:10.1056/NEJMr1507771, at p. 1254.

¹⁷ Koob *et.al*, "Neurocircuitry," fn. 14, above, p. 223; Volkow ND, Fowler JS, Wang G-J, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry*. 2004;9(6):557-569. doi:10.1038/sj.mp.4001507 at p. 557

- a. Prior to 1980, doctors used opioid pain relievers sparingly, and only for the short term in cases of severe injury or illness, during surgery, or at the very end of life.¹⁸ Doctors' reluctance to prescribe opioids stemmed from the legitimate concern that patients would get addicted.
 - i. Awareness of the risks of addiction caused by opioids ingested in the context of medical care, dated back at least to the Civil War, when injured soldiers became addicted to morphine, and heroin was available over the counter next to Bayer aspirin as a cough and cold remedy, leading to the opioid epidemic of the early 1900s.¹⁹(
 - ii. A study published in 1954 reported that 27% of opioid addicted white males (137/508) and 1.2% of African American males (4/330) yielding a combined rate of 16.8% (141/838), became addicted after being treated with opioids for pain. The authors successfully tapered these patients off of opioids, with improved pain and function in more than 80%. The authors concluded, "Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures."²⁰
 - iii. This history contributed to the longstanding reluctance of the medical profession to prescribe opioids prior to the marketing campaigns carried out by the Defendants as described below.
- b. Opioid prescribing tripled between the 1990's and 2012, and dramatically increased in dose and duration. "By 2010, enough OPR [opioid pain relievers] were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month."²¹

¹⁸ Meldrum ML. *Opioids and Pain Relief: A Historical Perspective (Progress in Pain Research and Management, V. 25)*. IASP Press; 2003, at pp. 195-199.

¹⁹ Courtwright DT. *Dark Paradise: A History of Opiate Addiction in America*. Harvard University Press; 2001, at pp. 45-46; 89-91.

²⁰ Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA - J Am Med Assoc*. 1954;156(7):684-691, at p. 690.

²¹ Paulozzi LJ, Jones CM, Mack K a, Rudd R a. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- {United States}, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487-1492, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w, at p. 1489.

- i. From 1996 to 2011 there was a 1,448% increase in the medical use of opioids, with increases of 690% from 1995 to 2004 and 100% from 2004 to 2011. Over the same time period, opioid misuse increased more dramatically: 4,680% from 1996 to 2011, with increases of 1,372% from 1996 through 2004 and 245% from 2004 to 2011. The number of patients seeking treatment for opioid use disorder in this time period, not including heroin, increased 187%, whereas treatment-seeking increased 87% for heroin, 40% for marijuana, and decreased 7% for cocaine.²² The increase in the medical use of opioid analgesics during this time period contributed to increases in misuse and addictive use.
- ii. “By 2005, long-term opioid therapy was being prescribed to an estimated 10 million US adults. The volume of prescribed opioid analgesics was 100 MME per person in 1997; in 2007, the MME per person had increased to almost 700 MME.”²³ (A very recent study found that the 2017 level of MME had declined from its peak to 543.4 MME, which remains well over 5 times higher than the prescribing rate in 1997.²¹
- iii. The number of long-term opioid users (daily for greater than 90 days) increased between 1999 and 2014. “Of all opioid users in 2013-2014, 79.4% were long-term users compared with 45.1% in 1999-2000.”²⁴ The increase in long-term use is important, because increased duration of use is also directly correlated with risk of addiction.²⁵
- iv. Between 2006 and 2015, 66% of patients receiving an opioid prescription in an ambulatory (outpatient) care setting had a diagnosis of non-cancer pain, and 28% had no pain diagnosis at all. Only 5% of patients had a cancer-related pain diagnosis. Absence of a pain diagnosis was more common in visits where an opioid

²² Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician*. 2014, at p. E119.

²³ Paulozzi LJ, Weisler RH, Patkar A a. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *J Clin Psychiatry*. 2011;72(5):589-592.

doi:10.4088/JCP.10com06560, at p. 589; for 2017 figures, see Schieber LZ, Guy, GP, Seth P, et al. Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017. *JAMA Netw Open*. 2019;2(3):e190665, at p. 1.

²⁴ Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf*. 2017. doi:10.1002/pds.4278, at p. 526.

²⁵ Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals With Chronic Noncancer Pain. *Clin J Pain*. 2014;30(7):557-564, at p. 557.

prescription was continued (30.5%) than those in which an opioid was newly prescribed (22.7%).²⁶

- v. As reported in an article I co-authored in 2016, more than one-third of Part D Medicare enrollees fill at least one opioid prescription in any given year. Part D covers 68% of the roughly 55 million people on Medicare.²⁷ As such, more than 10 million Part D Medicare enrollees are exposed to a prescription opioid in any given year, thus becoming vulnerable to the adverse effects of opioids, including but not limited to addiction. Medicare represents just one patient population, suggesting that many millions of patient consumers in this country have been exposed to the risks of prescription opioids in recent decades, both within and outside the Medicare-eligible populations. As discussed later in this report, much of that exposure resulted from aggressive marketing that overstated benefits and downplayed risks of chronic exposure to prescription opioids.
- c. As reported in another article I co-authored in 2016, increased opioid prescribing is distributed across different types of prescribers, relatively indifferent to individual physicians, specialty or region.²⁸ In other words, opioid overprescribing is not the result of a small subset of so-called ‘pill mill’ doctors, although such doctors do exist, but rather has been driven by a wholesale shift in medical practice. All doctors across diverse medical specialties are prescribing more opioids.
 - i. By specialty, pain doctors prescribe more opioids than doctors in any other specialties. However, by volume, family medicine and internal medicine doctors account for the most opioids, simply because there are more of them.²⁹
 - ii. But the salient finding was that opioid prescribing is not driven by a minority of prolific prescribers.³⁰
- d. Although national average opioid prescribing has plateaued or decreased since its peak in 2012, there are still many cities, counties, and states across the nation where opioid prescribing continues to be high, and overall opioid prescribing in the US remains at levels far exceeding pre-1990 rates.

²⁶ Sherry TB, Sabety A, Maestas N. Documented Pain Diagnoses in Adults Prescribed Opioids: Results From the National Ambulatory Medical Care Survey, 2006–2015. *Ann Intern Med.* 2018;169(12):892-894, at p. 892.

²⁷ Lembke *et al.*, “Use of Opioid Agonist Therapy”, fn. 5, above, at pp. 990-991.

²⁸ Chen *et al.*, “Distribution of Opioids”, fn 4, above, at p. E2.

²⁹ *Id.* at pp. E1-E2.

³⁰ *Id.* at p. E2.

- i. The U.S. national average number of opioid prescriptions written in 2012 was 81 opioid prescriptions per 100 persons (255 million total prescriptions). By 2016, the U.S. national average had decreased to 66 opioid prescriptions per 100 persons (214 million total). In 2017, the prescribing rate had fallen to its lowest in more than 10 years, at 59 prescriptions per 100 persons (total of more than 191 million total opioid prescriptions).³¹
- ii. However, prescribing rates continue to remain very high in certain areas across the country. In 2017, according to the CDC, “In 16% of U.S. counties, enough opioid prescriptions were dispensed for every person to have one.” And “some counties had rates that were seven times higher than that.”³²
- iii. In Summit County, Ohio, 98 opioid prescriptions were written per 100 persons in 2012.³³ In 2017, that number decreased to 62 opioid prescriptions per 100 persons, still above the national 2017 average.³⁴
- iv. In Cuyahoga County, Ohio, 76 opioid prescriptions were written per 100 persons in 2012.³⁵ In 2017, that number decreased to 50 opioid prescriptions per 100 persons, below the national average,³⁶ but still many times greater than prescribing rates in the early 1990’s.
- v. Among 48 million individuals with any period of insurance coverage between January 2007 and December 2016, including commercial beneficiaries, Medicare Advantage beneficiaries aged 65 years and over, and Medicare Advantage beneficiaries under age 65 years (eligible owing to permanent disability), data show that prescription opioid use and average daily dose measured at the individual level have not substantially fallen from their peaks. “Across all years of the study, annual opioid use prevalence was

³¹ Centers for Disease Control and Prevention. *U.S. Prescribing Rate Maps*.
<https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>

³² *Id.*

³³ Centers for Disease Control and Prevention. *U.S. County Prescribing Rates, 2012*. *Maps*,
<https://www.cdc.gov/drugoverdose/maps/rxcounty2012.html>

³⁴ Centers for Disease Control and Prevention. *U.S. County Prescribing Rates, 2017*.
<https://www.cdc.gov/drugoverdose/maps/rxcounty2017.html>

³⁵ CDC, 2012 Maps, fn. 33, above.

³⁶ CDC, 2017 Maps, fn. 34, above.

14% for commercial beneficiaries, 26% for aged Medicare beneficiaries, and 52% for disabled Medicare beneficiaries.”³⁷

3. The Pharmaceutical Opioid Industry increased sales of prescription opioids by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like The Joint Commission, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread opioid prescribing. These actions directly contributed to the opioid epidemic we face today.

a. Key opinion leaders

- i. To encourage doctors to prescribe more opioids, opioid manufacturers promoted the careers of physicians who were sympathetic to their cause. They singled out vocal proponents of liberal opioid prescribing, especially for chronic pain conditions, and paid these physicians to promulgate the benefits of opioids while minimizing the risks.³⁸
- ii. These “thought leaders” and others, including the Defendant manufacturers, actively promoted a 1980 *New England Journal of Medicine* Letter to the Editor by Porter and Jick, entitled “Addiction Rare in Patients Treated with Narcotics.”³⁹ Porter and Jick described that among hospitalized patients taking opioids for pain, they found only four cases of addiction among 11,882 patients treated with opioids. This letter was used as evidence by Defendants and key opinion leaders to argue that opioid addiction is rare in the course of medical treatment, despite the fact that the so-called evidence was of poor quality and not representative of patients seen in usual clinical care. The catch phrase “less than 1% get addicted,” based on this one data point, was used in branded advertisements by opioid manufacturers. (See Appendix I on promotional material.)
- iii. Significantly, the population in question in the Porter and Jick article is described as “hospitalized,” and receiving at least one dose of an opioid, without any reference to the size of the dose or range of duration of exposure. There is no reasonable basis to compare the risk of addiction among hospitalized patients who may have received only a single dose or short term course of

³⁷ Jeffery MM, Hooten WM, Henk HJ, *et al.* Trends in opioid use in commercially insured and Medicare Advantage populations in 2007-16: retrospective cohort study. *Bmj.* 2018;362:k2833. doi:10.1136/bmj.k2833, at p. 1.

³⁸ Saper JR. The Influence of Pharma and Device Manufacturers on APS and other PMAs: A War Within a War. *Exhib 6 to Saper Depos*, at 3-4.

³⁹ Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med.* 1980;302(2):123.

opioid medication, with the far greater risk among patients prescribed opioids for non-cancer chronic pain, outside the hospital setting. This is especially true in light of the well-known relationship between longer duration of opioid exposure and increased risk of dependence and abuse.

- iv. As Edlund *et al.* state, “Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially.”⁴⁰ For low dose (1-36 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).⁴¹
- v. These data from the Edlund study show that both dose and duration affect the risk of opioid use disorder. That is, the higher the dose, the greater the risk; and the longer the duration of exposure; the greater the risk. When both higher dose and longer duration are found, patients are 120 times more likely to suffer from opioid use disorder than patients who were not prescribed opioids.
- vi. Despite the lack of reasonable or scientific basis for using Porter and Jick to support the concept of the “rarity” of addiction, Defendants and their key opinion leaders frequently cited this letter to the editor as if it provided sound scientific support for wide prescribing of opioids. (See Appendix I on promotional material.)
- vii. Other articles cited by key opinion leaders and Defendants on low addiction rates in pain patient populations, included a national survey of burn facility staff with knowledge of >10,000 burn patients administered opioids, with no cases of iatrogenic addiction identified.⁴² Burn debridement, consisting of the removal of dead tissue to promote healing, is a short-term procedure carried out in a hospital setting. Mean administered morphine during the procedure

⁴⁰ Edlund, *et al.*, Role of Opioid Prescription,” fn. 25, above, at p. 561,

⁴¹ *Id.* at p. 559-60.

⁴² Perry, S, Heidrich, G, Management of pain during debridement: A survey of U.S. burn units. *Pain*. 1982;13(3):267-280, <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed1a&NEWS=N&AN=1982178505> . at. 267-77.

was only 8.9 mg, a very low dose. Although the authors referred to continued narcotic therapy after debridement, no details were provided regarding dose or duration, and burn healing is inherently a time-limited process unlike chronic arthritis, back pain, or other conditions for which Defendants promoted opioid therapy. As in the case of the Porter and Jick letter, the low risk of addiction for a short-term, hospital-based procedure and its limited sequelae are not comparable to the significant risk of addiction with long-term opioid therapy for chronic pain, and it is misleading to cite the burn study to support a claim of low addiction risk of opioids. Further, the study was not *a priori* designed to study addiction outcomes, and did not use rigorous methodology to study this outcome.

- viii. Defendants and their key opinion leaders also cited a survey study of a large headache clinic by Medina, *et al.*, in support of the claim that risk of addiction was low.⁴³ Sixty-two patients fulfilled criteria for inclusion in the study, in that they had been prescribed either a narcotic (codeine or propoxyphene), or a barbiturate (butalbital) or both. 38 of the 62 patients were treated with butalbital, a Schedule III medication in the class of barbiturates, and 6 were treated with propoxyphene (Darvon), a Class IV drug. The authors reported, “Eight were dependent; six physically addicted, two psychologically dependent and two were abusers.....There is danger of dependency and abuse in patients with chronic headaches” (p. 1; emphasis added). Reliance upon the Medina study to suggest absence of risk appears to contradict the interpretation of the data by the authors themselves, who explicitly acknowledged the dangers. The authors also used conflated definitions of dependence, addiction, and ‘abuse’ not consistent with other studies or with DSM criteria of any edition; however, the finding that two patients were “psychologically dependent” would generally have been considered equivalent to a diagnosis of “addiction” at the time of the Medina article. In addition, the study did not use objective criteria for tracking misuse, such as urine toxicology or collateral information from family or the prescription drug monitoring database, which would have increased the investigators’ likelihood of identifying aberrant behavior.
- ix. None of these surveys represents reliable evidence of a low risk of addiction to prescribed opioids, which even industry key opinion leader, Dr. Russell Portenoy conceded in 2011. In a taped interview with Dr. Portenoy in 2011, Portenoy described his promotion of opioids in the 1990s and early 2000s: “I gave so

⁴³ Medina JL, Diamond S. Drug Dependency in Patients with Chronic Headaches. *Headache J Head Face Pain.* 1977;17(1):12-14. doi:10.1111/j.1526-4610.1977.hed1701012.x, at pp. 1-2.

many lectures to primary care audiences in which the Porter and Jick article⁴⁴ was just one piece of data that I would then cite. I would cite 6 to 7 maybe 10 different avenues of thought or evidence, *none of which represents real evidence*. And yet what I was trying to do was to create a narrative so that the primary care audience would look at this information *in toto* and feel more comfortable about opioids in a way they hadn't before. . . . Because the primary goal was to de-stigmatize, *we often left evidence behind*.”⁴⁵ (Emphasis added.)

b. Continuing medical education

- i. The practicing physician relies on continuing medical education (CME) conferences to acquire state of the art knowledge about the latest scientific evidence in medical practice. The average clinician busy seeing patients cannot wade through the voluminous literature him or herself. Instead, (s)he attends CME conferences, and assumes that the knowledge disseminated there, especially by esteemed academic colleagues, represents unbiased research. The FDA hires independent auditors to review CME courses to make sure they're following a blueprint and are free of pharmaceutical influence, but auditors are required to audit no more than 10% of all CME.⁴⁶ (See discussion of one example of an opioid CME designed by Mallinckrodt, in Appendix I)
- ii. Drug company-sponsored continuing medical education (CME) preferentially highlights the sponsor's drug(s) compared with other CME programs. The average physician attending CME courses underestimates the influence of industry-sponsored speakers and industry-sponsored CME, which is considerable. Data show changes in prescriber practice in favor of the sponsor's drug, after participation in an industry sponsored CME event.⁴⁷
- iii. Not only has drug-company involvement in continuing medical education programs become prolific generally over the past several decades, but Defendants employed CME as part of the strategy to deploy their message about opioids starting in the late 1990s and continuing to today.⁴⁸

⁴⁴ Porter, Jick, *et al.*, “Addiction Rare,” fn. 39, above.

⁴⁵ Lurie J. Doctors Receive Opioid Training. Big Pharma Funds It. What Could Go Wrong? *Mother Jones*. <https://www.motherjones.com/politics/2018/04/doctors-are-required-to-receive-opioid-training-big-pharma-funds-it-what-could-go-wrong/>.

⁴⁶ *Id.* at p. 3.

⁴⁷ Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? *JAMA*. 2000;283(3):373-380. <http://dx.doi.org/10.1001/jama.283.3.373>, at pp. 373, 377-78.

⁴⁸ Saper, “The Influence of Pharma,” fn.38, above, at p. 2.

- iv. I have personally experienced this CME strategy. For example, in 2001, every licensed physician in the state of California was mandated to attend a day-long CME course on the treatment of pain as a requirement to maintain licensure. I attended that day-long course, in which use of opioids was promoted. I recall that there was no accurate presentation of the risks of opioids, and the messages that were provided tracked the misconceptions described above regarding overstatement of the benefits of opioids.
- v. Consistent with and supportive of my personal experience, Dr. Joel Saper, a past board member of the American Pain Society (APS), testified that “the educational programs of AAPM [American Academy of Pain Management] and APS particularly as they involve opioid advocacy, were greatly influenced by commercial largess. In my opinion, commercial dynamics influenced, if not steered, the selection of abstracts, course topics, and faculty to commercially friendly participants as it involved opioid advocacy, largely ignoring those imposing or exhorting caution against the growing advocacy for opioids for chronic nonmalignant pain.”⁴⁹ Dr. Saper testified that such educational programs of AAPM and APS involving opioid advocacy were “inappropriate”⁵⁰, and I agree.
- vi. Dr. Saper further stated that “APS and AAPM and its members have participated, if not promoted, this crisis by failing to assure the presentation of unbiased, balanced educational programs and guideline development, thereby protecting the public from commercial influence through undisclosed support from the opioid industry. In failing to do so, the organizations failed to protect patients.”⁵¹
- vii. Further, an internal Purdue Pharma email from Richard Sackler to Paul Goldenheim, dated April 13, 2001, concerned a planned meeting with “leaders of APS, APF [American Pain Foundation] and other pain societies.” Dr. Sackler stated, “Our goal is to bind these organizations more closely to us than heretofore, but also to align them with our expanded mission and to see that the fate of our product(s) are [sic] inextricably bound up with the trajectory of the pain movement.”⁵²
- viii. The use of “Speakers Bureaus” of doctors, trained by a drug company to promote its product, is an adjunct to the CME strategy.

⁴⁹ Deposition of Joel R. Saper, M.D., January 11, 2019, MDL No. 2804, at 92:13-22.

⁵⁰ *Id.* at 93:15-19.

⁵¹ *Id.* at 115:24-116:6

⁵² PPLPC045000004928- PPLPC045000004933 at 4929.

“From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses paid symposia, where they were recruited and trained for Purdue’s national speaker bureau. It is well-documented that this type of pharmaceutical company symposium influences physicians’ prescribing, even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns.”⁵³

- ix. These documents and testimony support my opinion that the Pharmaceutical Opioid Industry improperly supported the pro-opioid mis-education of medical professionals in order to increase sales of prescription opioids that resulted in an unprecedented epidemic of drug-induced mortality and morbidity. As I have written and stated elsewhere, doctors must bear some responsibility for the over-prescribing of opioids for chronic pain. However, the Pharmaceutical Opioid Industry bears the far greater share of the responsibility, for its role in promoting false messages of substantial benefit and low risk of opioids that influenced doctors to prescribe.
- c. The Joint Commission sold industry-produced teaching materials to hospitals.
 - i. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), often simply referred to as “The Joint Commission” (TJC), is a United States–based nonprofit tax-exempt 501(c) organization that accredits health care organizations and programs in the United States. The Joint Commission arose out of a movement in the 1950s to reform hospitals by looking at whether or not patients got better. JCAHO went through a consolidation of power over the years, combining multiple medical organizations under one roof, simplifying its name in 2007 to “The Joint Commission.” Its positioning statement is “Helping Health Care Organizations Help Patients.”⁵⁴
 - ii. Today, having Joint Commission accreditation is required for many hospitals and clinics to remain licensed. Payment for services from the Centers for Medicare and Medicaid Services (CMS), the largest federally funded insurance program, is also

⁵³ Van Zee A. The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. *Am J Public Health*. 2009. doi:10.2105/AJPH.2007.131714, at pp.221-22.

⁵⁴ The Joint Commission. <http://www.jointcommission.org/>. Accessed September 2, 2015.

contingent on TJC approval. TJC approval is obtained through periodic surveys.

- iii. The Joint Commission sold educational materials to hospitals so they could meet the standards of pain treatment that would be required to pass the next Joint Commission Survey. These materials included laminated cards and posters of the Visual Analog Scale of pain, as well as teaching videos promoting more liberal prescribing of opioids for pain, including misleading statements such as: “Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance and risk of death. . . . This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control.”⁵⁵ Per the GAO 2003 report, “During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff on how to comply with JCAHO’s pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO’s pain management educational programs. Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO’s Web site. Purdue’s participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin.”⁵⁶
- iv. On December 31, 2000, an internal Purdue email from Robin Hogen to Mortimer Sackler, MD, responded to Dr. Sackler’s assertion that more articles were needed “to help counteract the negative articles in the national media.” Hogen’s email, re press coverage of JCAHO pain guidelines, stated, “With respect to generating more articles about pain guidelines, we ‘loaned’ JCAHO our PR firm (Fleishman Hillard) last year during the national roll out of the new standards. I suspect some of these stories which are now breaking at year-end were generated by media contacts made several months ago. We could certainly renew that grant (\$75k) this year- to generate as much positive, unbranded publicity about the new pain standards and the chronic undertreatment of pain in America. Good idea.” This exchange supports my opinion that the Pharmaceutical Opioid Industry played a significant, insidious role in the epidemic of over-

⁵⁵ Catan T, Perez E., A Pain Drug Champion Has Second Thoughts. *The Wall Street Journal*. December 2012, at p.4.

⁵⁶ GAO. Prescription OxyContin Abuse and Diversion and Efforts to Address the Problem. *J Pain Palliat Care Pharmacother*. 2003;18(3):109-113. doi:10.1300/J354v18n03_12, at p.23.

prescribing of opioids, by funding the widespread promotion of standards that mandated pain treatment, while the medical profession and the public were unaware of Industry's hidden role.⁵⁷

4. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy. The Industry further claimed that the failure to prescribe opioids led to the 'undertreatment of pain.' Whether or not pain was undertreated does not change the fact that prescription opioids are an inappropriate method to address that concern, due to the absence of evidence of long-term benefit, and the strong evidence of unacceptable risk. Further, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment.

- a. Scientific evidence of prescription opioids' benefit for chronic pain has been repeatedly described as "weak," or "inconclusive." Randomized, placebo-controlled clinical trials, generally 12 weeks or less, were too brief to support claims of long-term benefit, and non-randomized trials do not provide reliable evidence of efficacy. Such evidence was inadequate to support the widespread use of the drugs and the risks they imposed. Even the 2009 Guidelines promulgated by advocacy groups funded by the Pharmaceutical Opioid Industry admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."⁵⁸ Twelve-week studies of opioids are insufficient to assess their risks and benefits, for the following reasons:

- i. Prescription opioids differ from other pain medications in important ways. In addition to providing acute pain relief, opioids also have unintended psychotropic effects (improved mood, increased energy, decreased anxiety), which make them more likely to be reinforcing and to lead to addiction. Patients with chronic pain can find opioids reinforcing, independent of whether they provide pain relief.³⁶ (p. 8) Although addiction to opioid painkillers can occur quickly in some individuals, for others, addiction may take weeks or months to manifest, and duration of exposure is the most significant risk factor for addiction (see discussion of Edlund study,²⁰ above). Hence, a true assessment of the risks of highly addictive drugs like opioid pain relievers, (the

⁵⁷ PDD8801183361- PDD8801183364 at 3363

⁵⁸ Chou R. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Pain*. 2009;10(2):[113-130](#) at p. 130.e5.

molecular equivalent of heroin), requires a longer period of study than 12 weeks.

- ii. There are serious and certain risks associated with long term opioid therapy, including but not limited to tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, serious constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, depression, addiction, accidental overdose, and death, reflecting a low benefit to risk ratio for long term opioid therapy.⁵⁹ These risks increase with increasing dose and duration of the drug.⁶⁰ Hence, the high risks associated with opioids, necessitate a longer study period to assess the true benefit-risk ratio for all patients.
- b. A series of reviews, including several in the Cochrane Database, have reached similar conclusions regarding the inadequacy of the scientific evidence of long-term opioid therapy for chronic non-cancer pain.
 - i. The 2010 Cochrane (Noble 2010) review found that there was only “weak” evidence to support the use of opioids for chronic non-cancer pain.⁶¹
 - A. “All of the evidence bases considered in this systematic review were of low internal validity and therefore at potentially high risk of bias.” Reasons for this assessment included the funding source (“Only two studies did not clearly have a funding source with a potential conflict of interest in the findings (e.g., drug company) [p. 9],” failure to compare characteristics of dropouts to those of patients who completed the studies; and failure to describe recruitment methods. The highest risk of bias existed for the “continuous outcomes” of pain relief and quality of life, because “high attrition rates affect both the risk of bias and the generalizability of the results from the continuous data outcomes.”⁶²

⁵⁹ Lembke *et al.*, “Weighing The Risks,” fn. 3, above, at p. 985; *see also* Chou R, Deyo R, Devine B, *et al.* The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. *Evid Rep Technol Assess* (Full Rep). 2014;218(218):63. doi:10.23970/AHRQEPERTA218 at p. ES-1; *see also* Edelman EJ, Gordon KS, Crothers K, *et al.* Association of Prescribed Opioids with Increased Risk of Community-Acquired Pneumonia among Patients with and Without HIV. *JAMA Internal Medicine*. 2018, at p. 298.

⁶⁰ Chou R, Turner J a., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4). doi:10.7326/M14-2559, p. 283

⁶¹ Noble M, Treadwell JR, Tregear SJ, *et al.* Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.

⁶² *Id.* at pp. 7-8.

- B. At pp. 9-14, specific data on attrition were provided: For the “strong opioid” category (categories described at p. 7), including extended release morphine, controlled release oxycodone, extended release oxymorphone, extended release tramadol and methadone; for oral medications, 34.1% discontinued due to adverse effects and 10.3% discontinued due to insufficient pain relief, for a total of 44.4% who discontinued strong oral opioids.⁶³
- C. The review states that only 273 (58%) of those who began the long-term extensions of short-term trials remained in the study at the 6-7.5 month cut-off point where data were available for all 3 oral opioid studies. “Because the attrition rate is so high, the participants are likely highly selected, and the data may be biased.”⁶⁴
- D. The authors report pain relief for those able to remain on oral opioids for 6 months; however: “The strength of the evidence supporting this conclusion is weak.”⁶⁵
- E. Quality of Life (QoL):
 - I. For oral morphine: A single study (Allan, 2005), reporting a “small improvement on the mental subscale and a larger improvement of the physical subscale” provided an “insufficient quantity of data from which to draw conclusions.”⁶⁶
 - II. QoL improvement was “weakly supported” with transdermal fentanyl (TDF).⁶⁷
 - III. For QoL with intrathecal opioids, there were inconsistent findings “No conclusions can be drawn.”⁶⁸
- F. “Data describing long-term safety and efficacy of opioids for CNCP are limited in terms of quantity and quality. An evidence base consisting of low-quality studies provides only *weak evidence* from which to draw qualitative

⁶³ *Id.* at pp. 9-14.

⁶⁴ *Id.* at p. 15.

⁶⁵ *Id.* at p. 16.

⁶⁶ *Id.* at p. 20.

⁶⁷ *Id.* at p. 21

⁶⁸ *Id.* at p. 22

conclusions and only low-stability evidence from which to draw quantitative conclusions.” (Emphasis added.)⁶⁹

G. “Despite the identification of 26 treatment groups with 4768 participants, the evidence regarding the effectiveness of long-term therapy in CNCP was too sparse to draw firm conclusions.”⁷⁰

ii. Another Cochrane Review of opioids in the treatment of chronic low back pain (CLBP) (Chaparro 2013) found, “There is some evidence (*very low to moderate quality*) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo.”⁷¹ (Emphasis in original.)

A. “The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks.”⁷²

B. “There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP.... We have no information from randomized controlled trials supporting the efficacy and safety of opioids used for more than four months. Furthermore, the current literature does not support that opioids are more effective than other groups of analgesics for LBP such as anti-inflammatories or anti-depressants.”⁷³

iii. Another Cochrane review (McNicol 2013) found: “While intermediate term studies all indicated that opioids were better than placebo, most studies were small, most were short, and none used methods known to be unbiased. All these features are likely to make effects of opioids look better in clinical trials than they are in clinical practice.”⁷⁴ Note that the McNicols review defined “intermediate” term studies as 35-84 days (ie, 5-12 weeks). Accordingly, these so-called intermediate studies are actually 12

⁶⁹ *Id.* at p. 23.

⁷⁰ *Id.* at p. 25.

⁷¹ Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev.* 2013. doi:10.1002/14651858.CD004959.pub4, at p. 2

⁷² *Id.*

⁷³ *Id.*

⁷⁴ McNicol E, Midbari A, Eisenberg E. Opioids for neuropathic pain (Review). *Cochrane Database Syst Rev.* 2013. doi:10.1002/14651858.CD006146.pub2, at p. 3

weeks or less, therefore too brief to provide data relevant to efficacy for chronic pain.⁷⁵

- iv. Another 2014 Cochrane review reached similar conclusions: “Similar to previous systematic reviews of randomized trials on opioid therapy for non-cancer pain [cites omitted], we found that most of the trials included in our review had a treatment duration of several days or a few weeks only.”⁷⁶
 - A. “Although some of the newer trials in the update had slightly longer treatment durations [cites omitted], in none of the trials did the participants receive opioids for longer than six months. This is still too short to address the impact of opioid treatment on routine clinical practice in the treatment of a chronic condition such as osteoarthritis. While no evidence of long-term effects is available from randomized trials, observational studies indicate that long-term treatment with opioids of chronic conditions such as osteoarthritis may have deleterious effects and do not seem to improve pain relief [citation omitted]”⁷⁷ (emphasis added).
 - B. Reviewers found that the “small mean benefit” was “contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI [confidence interval] did not include the minimally clinically important difference” on a visual analog scale.⁷⁸
- v. Chou *et al.* in their 2015 systematic review on the effectiveness of opioids in the treatment of chronic pain stated: “Evidence is *insufficient* to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.”⁷⁹ (Emphasis added.) The authors reported that most placebo-controlled studies were less than 6 weeks, and none were over 16 weeks long. “We did not include uncontrolled studies for these outcomes; reliable conclusions cannot be drawn from such studies because of the lack

⁷⁵ *Id.* at p. 13.

⁷⁶ da Costa BR, Nuesch E, Kasteler R, *et al.* Oral or transdermal opioids for osteoarthritis of the knee or hip (Cochrane Review). 2014, at p. 28.

⁷⁷ *Id.*

⁷⁸ *Id.* at p. 2.

⁷⁹ Chou *et al.*, “Effectiveness and Risks – Systemic Review,” fn. 60, above, at p. 276.

of non-opioid comparison group and heterogeneity of the results.”⁸⁰

- vi. In 2009, Chou was the lead author of a panel made up of a majority of Industry-funded physicians and psychologists who promulgated Guidelines that allowed for the use of chronic opioid therapy; in the same publication, those authors admitted that evidence regarding chronic opioid therapy was “insufficient to assess effects on health outcomes.”⁸¹
- vii. In another systematic review of opioid and non-opioid medication for acute or chronic low back pain, Chou *et al.* found that evidence for opioids “remains limited to short term trials showing modest effects versus placebo for chronic low back pain.” Shortcomings of the studies included high attrition (30-60% in most trials) and “short follow-up” (one at 16 weeks, all others shorter).⁸² Authors also noted: “Trials were not designed to assess the risk for overdose or opioid use disorder because of relatively small samples, short follow up, and exclusion of higher risk patients; in addition, many studies used an enriched enrollment randomized withdrawal design which could underestimate harms.”⁸³ (See paragraphs 9a-d, below, for discussion of enriched enrollment study design).
- viii. In a systematic review and meta-analysis (Häuser, Schmerz, 2015) of open-label continuation trials up to 26 weeks in duration in patients with a variety of different chronic pain disorders, the authors state “... the risk of bias [for these studies] was high all studies were funded by the manufacturers of the drugs⁸⁴ average pain scores are unrepresentative of patient experience and of very limited utility⁸⁵ The positive effects of opioid in long-term open-label studies cannot be disentangled from those of co-therapies not controlled for, from unspecific (placebo) effects because of the lack of placebo group or from the spontaneous recovery because of the lack of no treatment group. The external validity of open-label extension studies was comprised [sic] by a highly selected group of patients without major medical disease or

⁸⁰ *Id.* at p. 280

⁸¹ Chou, *et al.*, “Clinical Guidelines,” fn. 58, above, at p. 130.e5.

⁸² Chou R, Deyo R, Friedly J, *et al.* Systemic pharmacologic therapies for low back pain: A systematic review for an American College of physicians clinical practice guideline. *Ann Intern Med.* 2017. doi:10.7326/M16-2458, at p. 483.

⁸³ *Id.* at p. 486.

⁸⁴ Häuser W, Bernardy K, Maier C. Long-term opioid therapy in chronic noncancer pain: A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. *Schmerz.* 2015. doi:10.1007/s00482-014-1452-0, at p. 4.

⁸⁵ *Id.* at p. 7

mental disorders. The self-selected group of patients who were willing to participate in the open-label extension studies does not permit a clear conclusion on the long-term efficacy of opioids in routine clinical care.”⁸⁶

- ix. Many studies used an enriched enrollment randomized withdrawal (EERW) study design, an inherently biased methodology which *a priori* favors opioids over placebo. EERW design selects patients who are predisposed to tolerate and prefer opioids, and hence are not reflective of the general clinical population.
 - A. Randomized, double blind, placebo-controlled trials of 12 weeks durations or less (15 studies total) of opioids in the treatment of chronic pain used to get FDA approval, relied on enriched enrollment design (Meske *et al.* 2018),⁸⁷ and hence were biased toward favoring opioids. Open-label continuation trials commonly included subjects who successfully completed the randomized controlled trial phase using an enriched enrollment design. Hence those who entered the open label phase included those who successfully tolerated opioids through the randomized controlled trial period, resulting in an additional layer of bias favoring opioids, and diminishing the applicability of the study results to real world conditions.
 - B. For example, of the 295 initial subjects in the study by Caldwell *et al.* (2002) 222 subjects were assigned to opioid groups and 73 were assigned to placebo.⁸⁸ A 4-week randomized controlled trial (RCT) preceded an open-label phase; 40% of the opioid group who participated in the RCT dropped out due to adverse effects or inadequate pain relief,⁸⁹ and only those who lasted the full four weeks were permitted to enter the open-label phase. Of the 184 subjects who entered the open-label phase, 131 (72%) came from the opioid groups, while only 50 (28%) came from the placebo group; therefore, the open-label phase included a large majority of subjects who had demonstrated the capability to tolerate opioids, and the study’s claims of

⁸⁶ *Id.* at p. 8.

⁸⁷ Meske DS, Lawal OD, Elder H, Langberg V, Paillard F, Katz N. Efficacy of opioids versus placebo in chronic pain: A systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. *J Pain Res.* 2018. doi:10.2147/JPR.S160255, at pp. 923-934

⁸⁸ Caldwell JR, Rapoport RJ, Davis JC, *et al.* Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage.* 2002. doi:10.1016/S0885-3924(02)00383-4, at p. 283

⁸⁹ *Id.* at p. 283.

efficacy are not transferable to a real-world population. Despite the bias favoring opioid-tolerant subjects, more than half failed to complete the open-label phase; 95/181 (52.5%) discontinued.⁹⁰

- C. A meta-analysis of short term studies (< 6 weeks) confirmed a difference between enriched enrollment studies and non-enriched enrollment studies in terms of adverse medical consequences: “The incidence of adverse effects was noticeably different in the trials that used a classical non-EERW design from those that used the EERW design (Table 3). Among the trials with a non-EERW design, the number of reported adverse effects was 26, while among the trials with an EERW design, only eight adverse effects were reported.”⁹¹
- c. A recent (Busse 2018) metaanalysis confirms that there are no data to show clinically significant long-term efficacy of opioids in the treatment of chronic pain.⁹²
 - i. The primary study outcomes were “pain relief, physical functioning, and vomiting”.⁹³ The study defined the term Minimally Important Difference (MID) as “the smallest amount of improvement in a treatment outcome that patients would recognize as important.”⁹⁴ The data showed that opioid therapy failed to meet the MID as to the primary outcomes of pain relief and physical functioning, as well as the secondary outcomes of emotional functioning, social functioning, or sleep quality compared to placebo.⁹⁵
 - ii. For pain relief, the MID was defined as 1 cm on the 10 cm Visual Analog Scale (VAS); the data showed that the difference between opioid therapy and placebo was only 0.79 cm on the VAS, thus no minimally important difference was shown.⁹⁶ Despite not meeting the standard, the authors state, “Although the difference did not meet the minimally important difference of 1 cm, opioids were

⁹⁰ *Id.* at p. 286.

⁹¹ Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag.* 2011;16(5):337-351. doi:10.1155/2011/465281, at p. 347.

⁹² Busse JW, Wang L, Kamaleldin M. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA.* 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472.

⁹³ *Id.* at p. 2449.

⁹⁴ *Id.* at p. 2450.

⁹⁵ *Id.* at pp. 2451, 2455.

⁹⁶ *Id.* at p. 2451.

associated with pain relief compared to placebo....”⁹⁷ A more accurate statement would be that opioids were associated with a clinically insignificant difference in pain relief, since the change did not meet the study’s own definition of a clinically significant difference.. The study reported a difference of 2.80 favoring opioids over placebo on a 100-point scale for “role functioning;” however, “[w]hen restricted to trials reporting actual change, high quality evidence from 16 RCTs (5329 patients) demonstrated no association of opioids on role functioning compared to placebo.”⁹⁸

- iii. For the primary endpoint of vomiting, the opioid subjects had more than a 4-fold greater risk in nonenrichment trials, and a 2.5 times greater risk in enrichment trials, that is, trials in which subjects were pre-selected for greater ability to tolerate opioid therapy.⁹⁹
- iv. As for “Active Comparator” studies, the authors state: Moderate quality evidence [9 RCTs, 1431 patients] showed “no difference in the association of opioids versus nonsteroidal anti-inflammatory drugs for pain relief,” (emphasis added), and the same was true for physical function. The only significant difference was over 4-fold greater vomiting with opioids compared to NSAIDs (RR = 4.74, $p \leq 0.001$).¹⁰⁰
- v. Although the goal was to assess “chronic” non-cancer pain, the authors acknowledge that “it was not possible to assess the long-term associations of opioids with chronic non-cancer pain because no trial followed up patients for longer than 6 months.”¹⁰¹ (Emphasis added). There is some inconsistency in the literature about the definition of “chronic.” For example, the Cochrane Review (Noble, 2010) cites the International Association for the Study of Pain (IASP) for a definition of “pain which persists past the normal point of healing,” considered to be 3 months¹⁰²; however, on the very next page, the Cochrane review states that it considered only studies of at least six months, which it termed “Chronic opioid use...”¹⁰³ In any case, the Busse authors’ statement that it could not be applied to “long-term” use is an important limitation.
- vi. The Busse study states, “Studies with longer follow-up reported less relief,” which provides significant support for the reduced pain

⁹⁷ *Id.* at pp. 2451-2452.

⁹⁸ *Id.* at pp. 2451, 2455.

⁹⁹ *Id.* at p. 2455.

¹⁰⁰ *Id.*

¹⁰¹ *Id.* at p. 2457.

¹⁰² Noble, *et al.*, “Long Term Opioid Management,” fn 61, above, at p. 2.

¹⁰³ *Id.* at pp. 3, 6.

relief of opioids over time, and which buttresses the conclusion that even the minor “improvements” in pain and physical function shown in the studies compiled by Busse, which had a median of only 60 days’ follow-up,¹⁰⁴ cannot be extrapolated to longer term opioid use.

- vii. Three quarters of the studies 76 (79%) reported receiving industry funding.¹⁰⁵
 - viii. Despite these limitations, the authors concluded: “... some patients may find the modeled proportion of 12% for achieving the minimally important difference for pain relief warrants a trial of treatment with opioids.” The figure of 12% appears to represent the difference between the percentage who reported MID pain relief on placebo (48.7%) and those who reported MID pain relief on opioid therapy (60.6%); difference = 11.9%.¹⁰⁶
 - ix. In sum, the Busse analysis stands for the proposition that, by submitting to opioid therapy, the patient incurs significant and potentially fatal risks, in exchange for “benefits” that are found to be comparable to placebo for the large majority of subjects studied.
 - x. The pain relief MID standard adopted in the Busse study was at the low end of the spectrum of such study definitions, meaning that less improvement was required to meet the MID standard. A pooled analysis of multiple pain studies found that the average MID was 17 mm (1.7 cm) on the VAS scale, or over twice the 0.79 cm difference reported in the Busse meta-analysis.¹⁰⁷ Despite the lenient standard to show a difference that patients would notice, the Busse results failed that test.
- d. The SPACE randomized clinical trial study, published in JAMA in 2018, comparing opioid and non-opioid medication in the treatment of chronic pain, is the first long term (one year) randomized controlled trial of opioids in the treatment of moderate to severe pain, and found no benefit of opioids over non-opioid medication.¹⁰⁸

¹⁰⁴ Busse, *et al.*, “Opioids for Chronic Noncancer Pain,” fn 92, above, at p. 2451.

¹⁰⁵ *Id.* at p. 2451.

¹⁰⁶ *Id.* at p. 2456.

¹⁰⁷ Olsen MF, Bjerre E, Hansen MD, *et al.* Pain relief that matters to patients: Systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med. 2017. doi:10.1186/s12916-016-0775-3, at p. 10.

¹⁰⁸ Krebs EE, Gravely A, Nugent S, *et al.* Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. JAMA - J Am Med Assoc. 2018. doi:10.1001/jama.2018.0899

- i. The SPACE trial showed no benefit of opioids over non-opioid medication (NSAIDs, acetaminophen) in the treatment of moderate to severe chronic back, hip, or knee pain. The opioid group had significantly more adverse medication related symptoms.¹⁰⁹
- ii. The SPACE trial used a gold standard study design, as follows. It was 12 months in duration, a sufficient length to assess efficacy in the treatment of chronic pain. It included only patients not previously on long-term opioid therapy, and assessed preference for opioids prior to randomization, thereby eliminating the enriched enrollment bias evident in other studies. It used a naturalistic sample of patients in the primary care setting, including some patients with severe depression and post-traumatic stress disorder, the same patients who are often on high dose long term opioid therapy in real-life.¹¹⁰ Participants were regularly assessed for medication misuse, including checking the prescription drug monitoring database and urine drug testing.¹¹¹ It was not sponsored by an opioid manufacturer.¹¹²
- iii. It is very significant that a gold standard RCT, conducted by independent researchers and published in a leading medical journal (JAMA), reached an opposite result from those claimed by the Pharmaceutical Opioid Industry based on biased, short-term studies conducted by their own employees or paid consultants, and often published in specialty journals. The SPACE trial strongly supports my opinion that chronic opioid therapy does not provide greater long-term efficacy, rendering its high risks all the more unacceptable. Further, other studies have shown that opioids are no better than non-opioids for pain treatment.
 - A. In the Cochrane Review by Chaparro, *et al.*, discussed above, opioids were not superior to non-opioids for chronic low back pain.¹¹³
 - B. In a review of randomized head to head comparisons of opioids vs non-opioid pain relieving medication, non-opioids were found to be superior to opioids in terms of physical function and tolerability for short term (4-12

¹⁰⁹ *Id.* at p. 872.

¹¹⁰ *Id.* at p. 873

¹¹¹ *Id.* at p. 875.

¹¹² *Id.* at p. 881.

¹¹³ Chaparro, *et al.*, “Opioids Compared to Placebo,” fn 71, above, at p. 2.

weeks) therapy of neuropathic, low back, and osteoarthritic pain.¹¹⁴

- C. A systematic review comparing oral NSAIDS with opioids for treatment of pain due to knee osteoarthritis over at least 8 weeks' duration found opioids were no better than NSAIDs.¹¹⁵
- e. Despite the absence of reliable evidence for the use of long-term opioid therapy in the treatment of chronic pain, the Pharmaceutical Opioid Industry sought to shame prescribers into opioid prescribing, by claiming that the 'failure' to prescribe opioids was tantamount to causing pain, and to scare them into prescribing by suggesting reprisal from regulatory bodies like The Joint Commission. In their promotional material and "Train the Trainer" course, Defendants frequently invoked sources that characterized opioid prescribing as a moral obligation, and the failure to prescribe as the equivalent of causing pain, leading to Joint Commission and legal sanctions. Below are just a few examples. (See Appendix I for more detail.)
 - i. I remember that fear of 'undertreating pain' permeated medical practice and culture at this time. Doctors in some states were subject to the risks of disciplinary action from the board, and lawsuits that could follow, if they denied a patient's request for opioids.
 - ii. Joel Saper, M.D., a past board member of the American Pain Society (APS), testified that the American Pain Society (APS) received financial support from the Opioid Industry, which he referred to as "narcopharma. The American Pain Society, in turn, supported University of Wisconsin Pain and Policy Study Group (PPSG) professors David Joranson and June Dahl to "visit boards of medicine in state after to state to argue the importance of lessening the regulation of doctors who prescribe opioids for cancer, acute, and end-of-life pain."¹¹⁶
 - iii. In addition to the indirect support by the Industry through the APS, direct financial support to PPSG was provided by the Pharmaceutical Opioid Industry, as revealed in documents produced by PPSG and summarized in Appendix II to this Report.

¹¹⁴ Welsch P, Sommer C, Schiltenswolf M, Häuser W. Opioids in chronic noncancer pain-are opioids superior to nonopioid analgesics? : A systematic review and meta-analysis. *Schmerz*. 2015. doi:10.1007/s00482-014-1436-0, at p. 3.

¹¹⁵ Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. *Osteoarthr Cartil*. 2016. doi:10.1016/j.joca.2016.01.135, at p. 962.

¹¹⁶ Saper, "The Influence of Pharma," fn 38, above, at p. 9.

Those documents show substantial contributions by Purdue Pharma, Janssen, Endo, Ortho-McNeil, Alpharma, and Cephalon, over a period of over a decade, during which PPSG justified its recurring requests for further funding on the basis of its successful efforts to loosen restrictions on opioid prescribing by lobbying State Medical Boards, presentations at professional conferences, leading industry-friendly Continuing Medical Education seminars, and publications in the scientific literature. (See Appendix II to this Report).

- iv. The Pharmaceutical Opioid Industry and PPSG influenced states to adopt intractable pain laws that encouraged opioid prescribing by shielding physicians from liability. Although the statutes may have initially been intended for cancer, acute, and end-of-life pain, the statutes do not necessarily include any such limitations, and the Ohio statute did not restrict its protective shield to those circumstances. Intractable Pain Laws in various states, including Ohio,¹¹⁷ strengthened physicians' ability to prescribe opioids and also protected physicians from disciplinary action if the drugs were prescribed in compliance with the terms of the law.
- v. Ohio's Intractable Pain Law has since been revised to include a more involved series of steps that a prescribing doctor should take regarding discussion of the risks, monitoring the results, etc. Such belated restrictions were, however, insufficient to unwind the damage done by prior enactment of legislation that encouraged the increased prescribing of opioids. Notably, the PPSG documents include Ohio among the states whose pain laws were "improved" between 2000-2003, where "improvement" included loosening restrictions on opioid prescribing. (See Appendix II).
- f. Pain *improves* when patients on chronic high dose opioid therapy reduce their dose or come off of opioids.
 - i. A retrospective research study of patients consecutively admitted to the Mayo Clinic Pain Rehabilitation Center from 2006 through 2012, with a pain diagnosis of fibromyalgia, showed that patients tapered off of opioids had significant improvements in pain-related measures including numeric pain scores. The authors concluded, "this systemic review suggests that pain, function and quality of life may improve during and after opioid dose reduction."¹¹⁸

¹¹⁷ Ohio Admin. Code §4731-21

¹¹⁸ Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. Pain Med (United States). 2016. doi:10.1093/pm/pnv079, at p. 14.

- ii. A meta-analysis of opioid legacy patients (patients on long term opioid therapy as a ‘legacy’ of opioid prescribing in the 1990s) demonstrated that pain improves for many patients who decrease or go off of long term opioid therapy (LTOT). Sixty-seven studies were included in this analysis. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).¹¹⁹ The authors repeatedly note the need for more research and better quality evidence. Nonetheless, they conclude “several types of interventions may be effective to reduce or discontinue LTOT and that pain, function, and quality of life may improve with opioid dose reduction.”¹²⁰
- iii. In a study by Sullivan et al, high dose legacy patients were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N=35).¹²¹ The authors write, “It is important to note that the opioid dose reduction in both the taper support and usual care groups was achieved without a significant increase in pain severity. In fact, pain severity decreased on average from baseline to 22 weeks by approximately 1 point on the 0–10 scale in the taper support group and approximately a half-point in the usual care group. This finding is consistent with those in studies of inpatient pain rehabilitation programs, which have documented pain reduction with opioid dose reduction .”⁵⁷¹²²
- iv. A small outpatient study of opioid tapering in community patients showed no increase in pain intensity scores in patients who were able to taper their opioids by greater than 50% from the starting dose. The median opioid dose in the sample was 288 MED. The median duration of opioids was six years. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After four months, the median MED was reduced to 150 (IQR, 54-248) mg

¹¹⁹ Frank JW, Lovejoy TI, Becker WC, *et al.* Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. *Ann Intern Med.* 2017;167(3):181-191. doi:10.7326/M17-0598, at pp. 185-186.

¹²⁰ *Id.* at p. 181.

¹²¹ Sullivan MD, Turner JA, DiLodovico C, D’Appollonio A, Stephens K, Chan Y-F. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. *J Pain.* 2017. doi:10.1016/j.jpain.2016.11.003, at p. 308.

¹²² *Id.* at p. 318.

($P = .002$). Of note, neither pain intensity ($P = .29$) nor pain interference ($P = .44$) increased with opioid reduction.¹²³

- v. Many patients on chronic opioid therapy are reluctant to taper. In addition, some physicians and authors question whether tapering is necessary if the patient is stable and adherent to their current dose. Yet it is well established that patients on high doses of opioids are at increased risk for a variety of side effects, serious morbidities, and death.¹²⁴ Quality of life may be adversely affected, despite the fact that the patient perceives benefit in terms of pain relief. Indeed, as above, data show that in addition to reducing opioid-related risk, pain can improve when patients lower their opioids, which is evidence in and of itself that opioids do not work for chronic pain for those patients.
- g. Just as increased prescribing has been the cause of increased consumption and risk,¹²⁵ decreasing opioid prescribing decreases opioid consumption and risk. When doctors prescribe fewer opioids, patients consume fewer opioids, without increases in pain. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment, while at the same time reducing the risk of diversion of unused pills to unauthorized users.
 - i. In a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors concluded that such patients “need very little, if any, post-operative opioids.... Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction.”¹²⁶
 - ii. A case-control cohort study of 1,231 patients undergoing gynecologic oncology surgery, implemented an “ultrarestrictive opioid prescription protocol” (UROPP), resulting in a significant decrease in the number of opioids dispensed during the entire

¹²³ Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *JAMA Intern Med.* 2018. doi:10.1001/jamainternmed.2017.8709, at p. 708.

¹²⁴ Gomes T, Mamdani MM, Dhalla I a, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011;171(7):686-691. doi:10.1001/archinternmed.2011.117, at p. 686. See also Lembke *et al.*, *Weighing The Risks*,” fn 3, above, at p. 982; Edlund *et al.*, *Role of Opioid Prescription*,” fn 25, above, at p. 7; Chou *et al.*, *“Effectiveness and Risks,”* fn 60, above, at p. ES-1.

¹²⁵ Howard R, Fry B, Gunaseelan V, *et al.* Association of Opioid Prescribing with Opioid Consumption after Surgery in Michigan. *JAMA Surgery.* 2018, at p. E6.

¹²⁶ Shindo M, Lim J, Leon E, Moneta L, Li R, Quintinalla-Diek L. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. *JAMA Otolaryngology - Head and Neck Surgery.* 2018, at p. 1102.

perioperative period, without changes in postoperative pain scores, complications, or increases in the number of refill requests.¹²⁷

- A. The authors write, “For patients who underwent laparoscopic or robotic surgery, the mean (SD standard deviation) number of opioid tablets given at discharge was 38.4 (17.4) before implementation of the UROPP and 1.3 (3.7) after implementation ($P < .001$). After ambulatory surgery, the mean (SD) number of opioid tablets given at discharge was 13.9 (16.6) before implementation of the UROPP and 0.2 (2.1) after implementation ($P < .001$). The mean (SD) perioperative oral morphine equivalent dose was reduced to 64.3 (207.2) mg from 339.4 (674.4) mg the year prior for all opioid-naïve patients ($P < .001$).”¹²⁸
- B. “The significant reduction in the number of dispensed opioids was not associated with an increase in the number of refill requests (104 patients [16.6%] in the pre-UROPP group vs 100 patients [16.5%] in the post-UROPP group; $P = .99$), the mean (SD) postoperative visit pain scores (1.1 [2.2] for the post-UROPP group vs 1.4 [2.3] for pre-UROPP group; $P = .06$), or the number of complications (29 cases [4.8%] in the post-UROPP group vs 42 cases [6.7%] in the pre-UROPP group; $P = .15$).”¹²⁹
- h. In sum, the evidence for long-term opioid therapy for chronic non-cancer pain, going all the way back to Portenoy’s 1986 article,¹³⁰ was never more than “weak.” Such “weak evidence” was never sufficient to justify the aggressive promotion and resulting exponential increase in opioid prescribing for chronic pain. Moreover, the “weak evidence” based on flawed studies of the past has been refuted by strong, gold-standard randomized clinical trial evidence¹³¹ that opioids are *not* more effective than non-opioid pain relievers, while imposing greater risk.¹³² “Weak evidence” of benefit to a small minority of patients was never sufficient to offset the strong evidence of risk. Finally, and confirming the consensus of independent scientists, according to the National Academy of Science, Engineering, and Medicine (NASEM) 2017 Report, “Pain Management

¹²⁷ Mark J, Argentieri DM, Gutierrez CA, *et al.* Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. *JAMA Netw Open*. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452.

¹²⁸ *Id.* at p. 1.

¹²⁹ *Id.* at pp. 1-2.

¹³⁰ Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 Cases. *Pain*. 1986;25(2):171-186.

¹³¹ Krebs *et al.*, “Effect of Opioid,” fn 108, above, at p. 873; Welsch *et al.*, “Opioids in Noncancer Pain,” fn 114, above, at p. 3.

¹³² Krebs *et al.*, “Effect of Opioid,” fn 108, above, at p. 880.

and the Opioid Epidemic,” there is a “*lack of evidence that the drugs are effective for long-term pain management (VonKorff et al. , 2011).*”¹³³ (Emphasis added).

5. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate understatement of the risks of addiction to opioids. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain. There is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, “rare,” or “less than 1%.” In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 40%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction. So-called “abuse-deterrent formulations” do not lower the risk of addiction among patients taking them as prescribed.

- a. One of the biggest risk factors for becoming addicted to a substance is simple exposure to that substance. The current opioid epidemic is the most tragic and compelling example of that fact in modern history. As opioid prescribing has increased, and opioids have become more accessible to all Americans, opioid use has increased, and with it the rates of opioid addiction. The nearly quadrupling of opioid prescribing between 1999 and 2012 does not merely correlate with rising rates of opioid addiction and related deaths. It is causative. In their 2017 report “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,” The National Academies of Science, Engineering and Medicine stated, that despite FDA’s instruction to the panel that its task was not to assign blame for the current situation, “*certain hypotheses about causes of the epidemic are inescapable. For example, the data presented earlier in this chapter make a prima facie case that heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some) and substantially increased prescribing by physicians were key contributors to the increase in misuse, OUD, and accompanying harms.*”¹³⁴ (emphasis added)
- b. Likewise, decreased exposure to addictive substances decreases risk of addiction. Two natural experiments in the last century tested and proved this hypothesis. The first was Prohibition, a nationwide constitutional ban on the production, importation, transportation, and sale of alcoholic beverages from 1920 to 1933, which led to a sharp decrease in the number

¹³³ National Academies of Science Engineering and Medicine (NASEM). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.*; 2017. doi:10.17226/24781, at p. 29.

¹³⁴ *Id.* at pp. 40-41.

of Americans consuming and becoming addicted to alcohol.¹³⁵ (There were other unintended consequences of Prohibition, but the positive impact on alcohol consumption and related morbidity is widely under-recognized.) Second, many soldiers in Vietnam during the Vietnam War became addicted to opioids, most of whom stopped using opioids on their return to the United States, where access was limited.¹³⁶

- c. There is a clear link between prescription opioid exposure, prescription opioid misuse, and opioid addiction. Opioid misuse, or non-medical use of prescription opioids (NMUPO), is defined as taking an opioid medication other than prescribed. With increased opioid prescribing in the United States, more Americans have been exposed to prescription opioids at higher doses and for longer duration (including those not directly prescribed the opioid), contributing to rising incidence and prevalence of opioid misuse, dependence, and addiction.
 - i. In 2016, according to the National Survey on Drug Use and Health (NSDUH), more than 11 million Americans misused prescription opioids.¹³⁷ More than half obtained the misused prescription opioids from a friend or family member, who in most cases obtained them from a doctor. Thirty-five percent obtained misused prescription opioids directly from a single prescriber. Less than 10% of Americans misusing prescription opioids got them from a ‘street dealer.’¹³⁸ In other words, a medical prescription is the primary conduit for prescription opioid misuse. It should be noted that NSDUH data, by definition, are based on “households” and, as such, the data do not take into account misuse among homeless or incarcerated populations.
 - ii. The scientific literature shows that most lifetime nonmedical users of prescription opioids reported a lifetime history of medical use of prescription opioids, that is, most nonmedical users had current or previous legitimate prescriptions. “After controlling for other factors (e.g., gender, race, etc.) we observed an eight-fold increase (OR = 8.1, $p < 0.001$) in lifetime nonmedical use and a 10-fold increase (OR = 9.8, $p < 0.001$) in past year nonmedical use among

¹³⁵ Hall W. What are the policy lessons of National Alcohol Prohibition in the United States, 1920-1933? *Addiction*. 2010. doi:10.1111/j.1360-0443.2010.02926.x, at p. 105.

¹³⁶ Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *Am J Public Health*. 1974;64(12 Sup):38-43. doi:10.2105/AJPH.64.12_Suppl.38, at p. 40.

¹³⁷ Center for Behavioral Health Statistics and Quality. (2017). 2016 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD, at Table 1.97A.

¹³⁸ *Id.* at Table 6.53B.

students who had either current or previous prescriptions for pain medication.”¹³⁹

- iii. Teens are especially vulnerable to opioid misuse. In 2012, some 1.9 million individuals aged 12 or older misused a prescription drug for the first time within the past twelve months,¹⁴⁰ an average of 1,350 initiatives per day. Prescription drugs now rank fourth among the most-misused substances in America, behind alcohol, tobacco, and marijuana. They rank second among teens. Among teens who became addicted to any drug in the previous year, a quarter started out using a prescription medication: 17 percent began with opioid pain relievers, 5 percent with sedative-hypnotics, and 4 percent with stimulants.
- iv. McCabe *et al.* conducted a prospective national study of high school seniors in the U.S. to identify the sequence of medical versus non-medical use of prescription opioids, and the later development of a substance use disorder (addiction). They found that almost one in every two high school seniors who reported the medical use of prescription opioids after initiating NMUPO had two or more substance use disorder (addiction) symptoms at age 35.¹⁴¹
 - A. These data show that teens who are exposed to prescription opioids without a prescription, will often be further exposed through a subsequent medical prescription, and as a result are at increased risk of developing an opioid addiction later in life. The cumulative effect of prescription opioid exposure, through both medical and non-medical use, causally leads to opioid addiction.¹⁴²
 - B. The authors write, “These results indicate substantial risk for developing SUD among adolescents who have already initiated NMUPO and reinforce the critical role of screening when prescribing opioid analgesics to adolescents.”¹⁴³ While the authors suggest that screening can play a role in mitigating future opioid addiction,

¹³⁹ Boyd CJ, Esteban McCabe S, Teter CJ. Medical and nonmedical use of prescription pain medication by youth in a Detroit-area public school district. *Drug Alcohol Depend.* 2006. doi:10.1016/j.drugalcdep.2005.05.017, at p. 7.

¹⁴⁰ Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD; 2013., at p. 53.

¹⁴¹ McCabe SE, Veliz PT, Boyd CJ, Schepis TS, McCabe V V., Schulenberg JE. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend.* 2019. doi:10.1016/j.drugalcdep.2018.10.027, at p. 379.

¹⁴² *Id.* at p. 381.

¹⁴³ *Id.* at p. 383.

screening tools have been shown to have limited efficacy in identifying at risk patients.¹⁴⁴ The more significant goal is to reduce unnecessary and excessive opioid prescribing, which increases risk by increasing exposure to both medical and subsequent non-medical use.

- d. Even very limited exposure can result in addiction. A recent study of 14,888 persons aged 16 to 25 years-old who received an initial opioid prescription from a dentist, found that 6% were diagnosed with an opioid use disorder (OUD) within one year. For women in this group, the rate was 10%.¹⁴⁵ This study highlights the risk to teens and young adults, even after limited exposure to a dental procedure, such as removal of wisdom teeth.
- e. There are dozens of articles in the scientific literature that provide data on the risk of addiction, dependence, and/or misuse of prescription opioids in the course of medical treatment. In my opinion, these sources, individually and collectively, likely provide a significant underestimation of the true risk of misuse, dependence, and addiction for several reasons:
 - i. Many studies, particularly trials conducted by opioid manufacturers, screen out patients at higher risk of addiction, who are not commonly screened from real world clinical exposure.
 - ii. Many studies are not designed *a priori* to identify addiction outcomes, which means that they lack methodology to diagnose or otherwise accurately account for the cases.
 - iii. Many studies are sponsored and/or written by industry authors, raising conflict of interest and bias issues.
 - iv. Many studies are too short to assess addiction risk.
 - A. The natural history of addiction is that it takes some time to develop. Many people who become addicted start out using that substance to solve a problem, from anxiety to insomnia to physical pain. Over time, they become addicted to that substance. Although some become addicted very quickly, most become addicted over months to years, rather than days to weeks.

¹⁴⁴ Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pm/pnx332>, at p. 1382.

¹⁴⁵ Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. *JAMA Intern Med.* 2018, at p. E6.

- B. Risk of addiction to opioids increases with dose and duration of an opioid prescription. The higher the dose, and the longer patients are on them, the more likely they are to misuse opioids and become addicted. As previously stated, for low dose (1-36 MMEs per day) chronic exposure to prescribed opioids (*i.e.*, longer than 90 days), the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).¹⁴⁶ Because of the extraordinary increased risk of OUD with longer exposure, short-term studies are particularly ill-suited to assess that risk accurately.
 - C. Naliboff et al, in their two-arm, randomized, pragmatic clinical trial comparing stable dose to escalating dose of opioid medications among 135 patients at a VA clinic in Los Angeles, “carefully selected” as appropriate candidates for chronic opioid therapy, nevertheless discharged 27% of patients over the course of the study due to opioid misuse/noncompliance.¹⁴⁷ Urine toxicology screens were included in the protocol.¹⁴⁸ The authors concluded, “Overall, this study confirms that even in carefully selected tertiary-care patients, substance misuse is a significant problem. Importantly, *40% of these misuse problems did not become apparent within the first 6 months, pointing out the need for studies of longer duration.*”¹⁴⁹ (emphasis added)
- v. Many studies do not use rigorous detection methods
- A. Most studies rely solely on patient questionnaire responses to identify problematic behavior, despite generally accepted knowledge that a significant subset of respondents will not disclose behaviors of interest that could subject them to stigma, sanction, or both, as exemplified by the Fleming study (below).

¹⁴⁶ Edlund *et al.*, “Role of Opioid Prescription,” n 25, above, at pp. 559-560.

¹⁴⁷ Naliboff BD, Wu SM, Schieffer B, *et al.* A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain.* 2011;12(2):288-296. doi:10.1016/j.jpain.2010.09.003, at p. 288.

¹⁴⁸ *Id.* at p. 291.

¹⁴⁹ *Id.* at p. 295.

- B. A retrospective study of urine toxicology information for 122 patients maintained on chronic opioid therapy, found that 43% of patients had a “problem” with opioids: positive urine toxicology or one or more aberrant drug taking behaviors. The authors concluded “Monitoring both urine toxicology and behavioral issues captured more patients with inappropriate drug-taking behavior than either alone. Requiring a report of behavioral issues and urine toxicology screens for patients receiving chronic opioids creates a more comprehensive monitoring system than either alone.”¹⁵⁰
 - C. Urine drug tests provide more reliable evidence of drug misuse and addiction than patient report. Fleming found a 24% rate of positive toxicology tests for illicit drugs. “Eighty-four of 185 (46%) patients with positive toxicology testing denied illicit drug use during the research interview, even when they were guaranteed anonymity. This finding confirms clinical observations that patients with chronic pain often mislead their physicians about illicit drug use....Minimization of drug use and drug problems by patients is a major concern in all studies that try to estimate rates of addiction, especially for illegal drugs.”¹⁵¹ In other words, rates of opioid use disorder were potentially 8 times higher in the same population when objective measures of urine drug screens were used.
 - D. Databases with information on prescribing of controlled substances provide more reliable evidence of drug misuse and addiction than patient report. Checking a database with access to this information gives more reliable evidence on duplicate prescriptions, early refills, ‘doctor shopping,’ and other indicators of misuse and addiction.¹⁵²
- vi. Taking into account these limitations, it is my opinion that a 2015 article by Vowles, *et al.*, nevertheless provides the most reliable pooled estimate of the risk of addiction with chronic opioid

¹⁵⁰ Katz NP, Sherburne S, Beach M, *et al.* Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth Analg.* 2003. doi:10.1213/01.ANE.0000080159.83342.B5, at p. 1097.

¹⁵¹ Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. *J Pain.* 2007. doi:10.1016/j.jpaa.2012.02.008, at pp. 580-581.

¹⁵² <https://www.cdc.gov/drugoverdose/pdmp/states.html>

therapy.¹⁵³ In particular, the Vowles data synthesis prioritized studies using real world data designed to research opioid misuse and addiction. They also prioritized subjects from real world populations, rather than pre-screened clinical trial subjects enrolled in studies not designed to assess misuse or addiction. The authors adopted *a priori* criteria to assess study quality, and then checked their pooled results against the data from the highest quality studies. (By contrast, Fishbain et al, described below, completely excluded studies that did not meet their quality standards, which they admitted were arbitrary.) Further, Vowles, *et al.* disclosed that they had no conflicts of interest. (By contrast, Fishbain was an expert witness for Purdue in at least 3 cases between 2005-2008.¹⁵⁴) Because most available studies used patient questionnaires rather than objective urine drug screening, Vowles' analysis would represent a likely underestimate of addiction, despite a more appropriate selection of real world populations for the study.

- vii. In their systematic review and meta-analysis from 38 studies, Vowles, *et al.* cite a wide range of problematic prescription opioid use in patients being treated for a medical condition, ranging from <1% to 81% across studies.(p. 572) Across most calculations, rates of opioid misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%-38%), and rates of opioid addiction averaged between 8% and 12% (range, 95% CI: 3%-17%).¹⁵⁵
- viii. Even the lower risk classification of 8-12% would be considered a “very common” risk according to the World Health Organization and the Council of International Organizations of Medical Sciences:¹⁵⁶
 - A. Very common $\geq 1/10$
 - B. Common $\geq 1/100$ and $< 1/10$
 - C. Uncommon $\geq 1/1000$ and $< 1/100$
 - D. Rare $\geq 1/10,000$ and $< 1/1,000$

¹⁵³ Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van Der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*. 2015. doi:10.1097/01.j.pain.0000460357.01998.fl.

¹⁵⁴ *Graves v. Purdue Pharma* (N.D. Miss. 2008), Rule 26(a)(2) Disclosure of David A. Fishbain, M.D., 8/21/08, at pp. 1-8.

¹⁵⁵ Vowles *et al.*, “Rates of Opioid Misuse,” fn 153, above, p. 573.

¹⁵⁶ World Health Organization, CIOMS, http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf, at p. 10.

- E. Very rare < 1/10,000
- F. Although the US has not adopted a standard hierarchy like WHO/CIOMS, frequency of adverse events in product information material in the United States is consistent with the WHO standards: “rare” in US labels is commonly < 1/1000; “Infrequent” is >1/1,000 to < 1/100; and anything over 1/100 is “frequent.”¹⁵⁷
- ix. Vowles’ definition of “misuse” as culled from the included articles is consistent with the DSM-5 definition of mild opioid use disorder. As such, the prevalence of opioid use disorder in Vowles’ review using DSM-5 criteria is between 21-29%, including the spectrum from mild through severe OUD. (This is reasonably consistent with the Boscarino, *et al.* study¹⁵⁸ described below.)
- x. As with other meta-analyses, reports of misuse/addiction were higher in studies which relied on urine drug testing instead of self-report. For example, included in the Vowles analysis, a study by Brown, *et al.* demonstrated the lower rates based on self-report versus those based on urine toxicology.¹⁵⁹
 - A. This was a nonrandomized, open-label study of morphine sulfate ER (Avinza) for a titration period of 2-4 weeks followed by treatment for 12 weeks, administered to patients in primary care settings, evaluated for risk stratification and aberrant behaviors (including urine screening, early renewal requests, increased dose without authorization, oversedation).¹⁶⁰
 - B. Only 561 (38%) of the 1,570 originally enrolled patients completed the study, despite its relatively brief duration of 12 weeks of treatment. Of the 890 patients for whom reasons for withdrawal were provided, 410 (46%) included adverse events or failure of treatment among their reasons to withdraw. Five percent were asked to withdraw due to investigator assessment of “high risk level for drug

¹⁵⁷ Eriksson R, Aagaard L, Jensen LJ, *et al.* Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. *Pharmacol Res Perspect.* 2014;2(3):1-10. doi:10.1002/prp2.38, at p. 6.

¹⁵⁸ Boscarino J a, Rukstalis MR, Hoffman SN, *et al.* Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis.* 2011;30(3):185-194. doi:10.1080/10550887.2011.581961.

¹⁵⁹ Brown J, Setnik B, Lee K, *et al.* Assessment , stratification , and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. 2011;(December). doi:10.5055/jom.2011.0088.

¹⁶⁰ *Id.* at p. 468.

abuse/misuse” after enrollment, and another 5% for “noncompliance.”¹⁶¹

- C. The Vowles analysis incorporates the Brown study’s assertion that 2-3% of patients exhibited aberrant drug-related behaviors during visits 2 through 4, and 6% at visit 5, listing those percentages in the “misuse” column.¹⁶²
 - D. However, Urine Drug Screening (UDS) showed much higher rates of misuse and/or addictive use (although Vowles did not include these findings in his analysis): In particular, 17, 11, 11 and 15 subjects had positive UDS for oxycodone in weeks 2-5, despite prohibition of that drug after Visit 1.¹⁶³ By week 5, there were 79 subjects remaining in the study, and the 15 subjects with positive UDS for oxycodone yield a rate of 19% misuse and/or addictive use. This finding provides objective evidence that the prevalence of aberrant drug-related behavior was approximately 3 to 9 times the “2-6%” rate of aberrant drug related behaviors reported by the investigators¹⁶⁴ and cited by Vowles. Such use occurred despite patients having signed agreements to refrain from illicit drug use, and despite knowledge that UDS would be conducted.¹⁶⁵
 - E. Objective measures of addictive/aberrant behavior like drug screening results are more reliable than questionnaire responses, and these data from the Brown study support that view.
 - F. This study was Pfizer-sponsored. Authors included Pfizer/subsidiaries/consultants.¹⁶⁶
- xi. Also included in the Vowles analysis was a study by Fleming, *et al.*, again highlighting the discrepancy between self-report and urine toxicology.¹⁶⁷
- A. This Fleming article reported on substance use disorders among 801 chronic pain patients receiving daily opioid therapy from the same Wisconsin primary care practices that provided the population analyzed in the Fleming article

¹⁶¹ *Id.* at p. 473.

¹⁶² *Id.* at p. 572.

¹⁶³ *Id.* at p. 475, figure 2.

¹⁶⁴ *Id.* at p. 476.

¹⁶⁵ *Id.* at pp. 478-479.

¹⁶⁶ *Id.* at p. 481.

¹⁶⁷ Fleming, *et al.*, “Substance Use Disorders,” fn 151, above, at p. 579.

discussed above. Fleming reported a point prevalence of 3.8% for opioid use disorder and 9.7% for substance abuse and/or dependence, using DSM-4 criteria¹⁶⁸ and Vowles incorporated these percentages into the data synthesis.

- B. The diagnoses included in the percentages above were based on a 2-hour interview of each patient by the doctor or nurse at the primary care practice.¹⁶⁹ As referenced above, Fleming noted the large disparity between the patients' self-reporting of other drug use and the results of urine drug screening. There were 156 positive urine screens for cannabis compared to 106 self-reports, and 60 positive urine screens for cocaine compared to 24 self-reports.¹⁷⁰
- C. Although the article provided urine drug screen data on certain illicit drugs, sufficient to show the discrepancy between deceptive self-report and objective toxicology, the article did not provide data on the results of urine screens specifically for opioids, so there were no data to determine how many patients had more than expected (evidence of overuse), or opioids that were not prescribed (evidence of overuse), or less/no evidence of the prescribed opioids (evidence of possible diversion).
- D. Fleming also reported that "the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy compared with general population samples (3.8% vs 0.9%)."¹⁷¹
- E. Despite acknowledging the disparity between toxicology tests and diagnoses based on interview data, Fleming concluded that the "3.8% rate of opioid addiction is a small risk compared with the alternative of continuous pain and suffering. The data presented in this paper support the use of opioids for the treatment of chronic pain by primary care physicians."¹⁷² I disagree with this interpretation of the findings, especially in light of (a) the acknowledged disparity between the urine drug screen rate and the rate based on self-reports; (b) the unreliability of the latter; and (c) the unwarranted assumption that opioid therapy would

¹⁶⁸ *Id.* at p. 573.

¹⁶⁹ *Id.* at p. 574.

¹⁷⁰ *Id.* at p. 579.

¹⁷¹ Fleming, *et al.*, "Substance Use Disorders," fn 151, above, at p. 573.

¹⁷² *Id.* at p. 581.

alleviate chronic pain and suffering as a trade-off for accepting the risk of dependence or addiction.

- f. Boscarino, *et al.* published a study of addiction rates in a large population of patients receiving opioids to treat a medical condition, and found a 41.3% lifetime prevalence of opioid use disorder (using DSM-5 criteria).¹⁷³ The research in this study is strengthened by the fact that it was based on a random sample of outpatients seen in a large multispecialty group practice; that drug-use disorder was assessed based on the final DSM-5 criteria; and that subjects were identified through drug orders in the electronic health records, not based on patient self-report or treatment record. Weaknesses include the low survey response rate (33%).¹⁷⁴
 - i. “Using electronic records from a large US health care system, we identified outpatients receiving five or more prescription orders for opioid therapy in the past 12 months for noncancer pain (mean prescription orders =10.72; standard deviation =4.96). In 2008, we completed diagnostic interviews with 705 of these patients using the DSM-4 criteria. In the current study, we reassessed these results using the final DSM-5 criteria. Results: The lifetime prevalence of DSM-5 opioid-use disorders using the final DSM-5 criteria was 58.7% for no or few symptoms (2), 28.1% for mild symptoms (2–3), 9.7% for moderate symptoms (4–5), and 3.5% for severe symptoms (six or more). Thus, the lifetime prevalence of “any” prescription opioid-use disorder in this cohort was 41.3% (95% confidence interval [CI] =37.6–45.0).”¹⁷⁵
 - ii. “A comparison to the DSM-4 criteria indicated that the majority of patients with lifetime DSM-4 opioid dependence were now classified as having mild opioid-use disorder, based on the DSM-5 criteria (53.6%; 95% CI =44.1–62.8). In ordinal logistic regression predicting no/few, mild, moderate, and severe opioid-use disorder, the best predictors were age 65 years, current pain impairment, trouble sleeping, suicidal thoughts, anxiety disorders, illicit drug use, and history of substance abuse treatment.”¹⁷⁶
 - iii. In my opinion, the moderate-severe categories of DSM-5 OUD are consistent with Vowles’ definitions of addiction, and the milder DSM-5 diagnoses are more consistent with Vowles’ definition of

¹⁷³ Boscarino J, Hoffman S, Han J. Opioid-use disorder among patients on long-term opioid therapy: impact of final DSM-5 diagnostic criteria on prevalence and correlates. *Subst Abuse Rehabil.* 2015;83. doi:10.2147/SAR.S85667, at p. 83.

¹⁷⁴ *Id.* at p. 86.

¹⁷⁵ *Id.* at p. 83.

¹⁷⁶ *Id.* at p. 83.

misuse. Accordingly, the totals of 13% “moderate to severe opioid use disorder” in Boscarino are consistent with Vowles’ findings of 8-12% “addicted”; further, Vowles’ finding of 21-29% “misuse” is reasonably consistent with Boscarino’s report of 28% with “mild opioid use disorder.” In other words, both of these publications are reasonably consistent in assessing the risk of opioid addiction, ranging from mild to severe, in a clinical population of patients receiving opioids.

- g. The 2008 review by Fishbain claimed that the risk of addiction from chronic use of prescription opioids is 3.27% overall; 0.19% if considering de novo opioid users only.¹⁷⁷ Overall, Fishbain included 67 studies in his review and analysis of various measures of addiction or abuse. With respect to the 3.27% / 0.19% addiction rates, Fishbain stated that he relied on a subset of 24 studies with a total of 82 addiction cases among 2,507 patients, identified in Appendix 1 to the article, accessed at the journal website. However, review of the Appendix 1 table shows only 23 studies with 81 addiction cases among 2173 patients, resulting in a prevalence of 3.73%, rather than 3.27%. These figures are not reliable indicators of true prevalence of OUD, for the reasons explained below.
 - i. The Fishbain analysis included studies that (a) were too short to accurately assess addiction risk; (b) administered low doses; (c) screened out patients at higher risk of addiction; (d) were not designed to identify addiction (e) did not apply rigorous detection methods; and (f) were sponsored and/or written by industry authors, raising conflict of interest and bias issues.
 - ii. Fishbain’s pooled analysis found substantially higher evidence of drug misuse/addiction (14.5%) when findings were based on the more objective measure of aberrant urine toxicology screens.¹⁷⁸
 - iii. Fishbain’s 2008 review omitted two studies from his 1992 review that had reported substantially higher prevalence than the pooled figure of 3.27% stated in the 2008 article. Studies by Evans, *Anesthesia* 1981; 36:597-602,¹⁷⁹ (reported 16% addiction in Fishbain’s 1992 article¹⁸⁰), and Katon, *Am J Psychiatry* 1985;

¹⁷⁷ Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? a structured evidence-based review. *Pain Med.* 2008;9(4):444-459. doi:10.1111/j.1526-4637.2007.00370.x, at p. 444.

¹⁷⁸ *Id.* at p. 450.

¹⁷⁹ Evans PJD. Narcotic addiction in patients with chronic pain. *Anaesthesia.* 1981;36(6):597-602. doi:10.1111/j.1365-2044.1981.tb10323.x.

¹⁸⁰ The Evans article states that the addiction rate was 7%, which appears to be based on 9 cases among the full study population of 130 subjects. (Evans at p. 600) Fishbain’s 1992 article states, “Of 56 chronic *benign* patients, 9 or 16% exhibited features of addiction.” (Fishbain 1992, Table 4, at 83; emphasis

142:1156-60, (reporting 18.9% addiction)¹⁸¹, both appeared in Fishbain 1992 but were omitted from Fishbain 2008. Further, the Evans study, in turn, cited to an article by Maruta, Mayo Clinic Proceedings 1976; 54:241-4,¹⁸² which reported an incidence of 24% addiction among a chronic pain population.¹⁸³ Fishbain 2008 stated that his search for relevant articles went back to 1966, so these three references would have been within the time period he searched. Fishbain was a litigation consultant for Defendant Purdue between at least 2005-2008, a relationship that was not disclosed in the 2008 article, and which casts the exclusion of the higher prevalence studies in a disturbing light.

- iv. Fishbain made an admittedly “arbitrary” decision to apply a 65% “quality score” requirement, despite his own reference to a source stating that studies with scores below 50% are generally not used.¹⁸⁴ The Tables in the Appendix to the Fishbain 2008 article provide the quality scores only for the studies that were included, but not for those that were excluded, so it cannot be determined whether the three higher prevalence studies were excluded for failure to meet the arbitrary quality score threshold, or for other reasons. Their absence from the 2008 review casts further doubt on its reliability.
- v. A study reviewed by Fishbain (Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the pain assessment and documentation tool. J Opioid Manage 2005; 1:5.), was co-authored by Portenoy.¹⁸⁵ In this study, 27 physicians who attended training sessions to serve on “a pain-oriented speakers’ bureau” applied a “Pain Assessment and Documentation Tool” (PADT) to 388 of their patients, with diverse pain syndromes, who had been on various regimens of chronic opioid therapy for at least 3 months.¹⁸⁶ The physicians reported their assessment that 5.93% (23/388) of

added). Thus, comparing the two articles, it appears that Evans included the 74 cancer patients, who had no reported cases of addictive behavior, in the total of 130 subjects. Conversely, Fishbain’s 1992 study explicitly studied “Drug Abuse, Dependence, and Addiction in *Chronic Pain Patients*,” (emphasis added); thus the figure of 16% (9/56) appears accurate.

¹⁸¹ Egan K, Katon W. Chronic Pain: Lifetime Psychiatric Diagnoses and Family History. Am J Psychiatry. 1985;(October):1156-1160, at p. 1157.

¹⁸² Note that the Maruta article was actually published in 1979, and the cite in the Evans article lists the incorrect year of publication.

¹⁸³ Maruta T., Swanson D., Finlayson, R. Drug Abuse and Dependence in Patients with Chronic Pain. Mayo Clin. Proc. 1979 (April):241-244, at p. 242.

¹⁸⁴ Fishbain, *et al.*, “What Percentage,” fn. 177, above, at p. 448.

¹⁸⁵ Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool. J Opioid Manag. 2005.

¹⁸⁶ *Id.* at p. 258.

their patients were addicted.¹⁸⁷ However, the doctors also reported that 19.3 % (75/388) engaged in 3 or more “aberrant drug-taking behaviors,” such as requests for early renewals, increasing doses without authorization, reporting lost or stolen prescriptions, obtaining medications from other doctors, declining physical/social/psychological function, over-sedation, etc.; and that 10.8% (41/388) engaged in 5 or more such behaviors.¹⁸⁸ Their conclusion of 5.93% addicted lacks validity for several reasons.

- A. Appendix 1 states: “Of the total sample 5.93% were thought to demonstrate opioid prescription abuse/ addition [sic].”¹⁸⁹ This is not correct, since the 5.93% applies solely to addiction, whereas the abuse rates were much higher, as described above.
 - B. Other studies on Fishbain’s reference lists would count such behaviors as evidence of addiction, such that the addiction rate in the Passik study would be about 2 to 4 times greater than the 5.93% rate based on the doctors’ reports. Including the full range of opioid use disorder (mild, moderate, severe) based on DSM-5 criteria, this study’s summative results (5.93% + 19.3% + 10.8%) demonstrate that 36.06% of patients met DSM-5 criteria for opioid use disorder, approximating the 40% rate of opioid use disorder consistent with the Boscarino, *et al.* study¹⁹⁰ described above.)
 - C. The possibility of underestimating addiction rate is of particular concern in light of the participating physicians’ roles as Speakers’ Bureau trainees.
- vi. In another study reviewed by Fishbain et al, 10 patients, who had been treated for chronic noncancer pain (CNCP) with morphine for an average of 2 years, participated in a study alternating between one 60 hour period of morphine and one 60 hour period of placebo (Two and a half days each).¹⁹¹ “When asked ‘Do you have any drug craving?’ (graded as mild, moderate or severe), no patients reported craving for morphine or a compulsion to take any,” during

¹⁸⁷ *Id.* at p. 263.

¹⁸⁸ *Id.* at pp. 260-261.

¹⁸⁹ *Id.* at Appendix I, p. 47.

¹⁹⁰ Boscarino, *et al.*, “Opioid-use disorder,” fn 173, above, at p. 83.

¹⁹¹ Cowan DT, Wilson-Barnett DJ, Griffiths P, Vaughan DJA, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Med.* 2005. doi:10.1111/j.1526-4637.2005.05020.x, at p. 113.

the period of cessation of opioids.¹⁹² Authors concluded from these data “that there exists a group of CNCP patients whose long-term opioid consumption can be beneficial and remain moderate without them suffering from the consequences of problematic opioid drug use.”¹⁹³ Appendix 1 states: “0% demonstrated psychological dependence.”¹⁹⁴ This conclusion lacks validity for several reasons.

- A. The short duration without opioids is insufficient to assess the presence of addiction. Addiction is a chronic relapsing and remitting illness evidenced by a pattern of behavior over weeks to months, not hours to days.
 - B. Craving and withdrawal are very subjective and not diagnostic of addiction. Further, asking study subjects about “craving” is likely to bias their response: ‘craving’ is a loaded term associated with addiction. Patients would be savvy enough to want to avoid this pejorative label.
 - C. This British study was funded by Janssen-Cilag, introducing inherent bias.¹⁹⁵
 - D. Although this is a small study that would have little overall impact on the pooled analysis, it is worth attention if only to demonstrate the contradiction between Fishbain’s inclusion of an almost absurdly brief study of 60 hours of exposure – not even enough time to develop dependence, let alone addiction—while omitting relevant studies with higher prevalence that he personally cited in his earlier review article.
- h. Higgins, *et al.* performed a meta-analysis of incidence of addiction studies, that is, addiction diagnosed in a pre-specified period of time following the initial exposure to a prescription opioid. The authors argued for a 4.7% overall incidence of iatrogenic addiction to prescription opioids,¹⁹⁶ but their findings need to be considered in light of a number of limitations.
 - i. Incidence will inevitably under-report the number of cases in a population, because it will only examine data for a fixed beginning and endpoint; whereas prevalence is the more accurate marker of

¹⁹² *Id.* at p. 116.

¹⁹³ *Id.* at p. 119.

¹⁹⁴ *Id.* at Appendix 1.

¹⁹⁵ *Id.* at p. 113.

¹⁹⁶ Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth.* 2018;120(6):1335-1344. doi:10.1016/j.bja.2018.03.009, p. 1339.

the number of cases existing in a population at a given point in time, including all cases of addiction among the population taking prescription opioids.

- ii. New onset opioid use disorder (incidence) does not take into account the harm done to patients who maintain or relapse to opioid addiction as a result of medical exposure to opioids. That is, continued exposure imposes continued risk of misuse, dependence, overdose, and the panoply of ill effects of chronic opioid therapy described herein.
- iii. The authors claimed that the pooled rate was higher for the studies of “weak” opioids than for “strong” opioids because the subjects might have displayed “pseudoaddiction,”¹⁹⁷ i.e., because the opioids were weak, they displayed drug-seeking behaviors to alleviate their pain that were misconstrued by the physicians, rather than because of a use disorder. The report of a higher rate with lower doses is an unreliable, outlier finding that contradicts numerous large, well-done studies demonstrating the dose-response relationship between higher opioid dose and more bad outcomes.
- iv. The authors’ restrictive criteria resulted in only 12 studies having been included¹⁹⁸ compared to others (e.g., Vowles), who included 38 studies.
- v. The authors erroneously stated that Vowles reached a similar conclusion as to the rates of addiction (4.3 v. 4.7%), (p. 1342) when in fact Vowles reported rates of addiction as 8-12%,¹⁹⁹ or approximately 21-29% when the spectrum of mild through severe OUD is included.
- vi. Two of three authors report pharma consulting, including Pfizer.²⁰⁰
- i. The 2010 Cochrane Review by Noble *et al.* (2010) claimed that opioid addiction occurred in “0.27% of participants in the studies that reported that outcome,”²⁰¹ and “... serious adverse events, including iatrogenic opioid addiction, were rare.”²⁰² These findings are specious for the following reasons:

¹⁹⁷ *Id.* at p. 1343.

¹⁹⁸ *Id.* at p. 1335.

¹⁹⁹ Vowles, *et al.*, “Rates of Opioid Misuse,” fn 153, above, at p. 569; McNicol, *et al.*, Cochrane Review 2013, fn 74 at p. 28.

²⁰⁰ Higgins, *et al.*, “Incidence of Iatrogenic,” fn 196, above at p. 1343.

²⁰¹ Noble, *et al.*, “Long Term Opioid Management,” fn. 61, above, at p. 9.

²⁰² *Id.* at p. 2.

- i. The Cochrane 2010 review analyzed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants. Twenty five of the studies were case series or uncontrolled long-term trial continuations. The other was an RCT comparing two opioids.²⁰³ Only 8 of the 26 included studies provided data on addiction: Allan; Anderson; Hassenbusch; McIlwain; Milligan; Mystakidou; Portenoy; and Zenz.
- ii. Only one of these studies (Portenoy, 2007)²⁰⁴ was *a priori* designed to assess risk of opioid use disorder/addiction. The rest were designed to assess pain efficacy, and addiction risk was an afterthought. Further, none applied rigorous detection methods, or in most cases any detection methods at all to assess opioid misuse or addiction. All of the studies excluded patients with a history of alcohol or substance use disorders. Seven of the eight studies were sponsored and/or written by industry authors, raising conflict of interest and bias issues.
 - A. Allan *et al.* compared efficacy and safety of transdermal fentanyl and sustained release morphine in opioid naïve patients with chronic low back pain over 13 months.²⁰⁵ Classification as ‘opioid naïve’ was based on the patient receiving limited opioids in the 4 weeks prior to the study, with no screening for opioid use prior to 4 weeks.²⁰⁶ Opioid misuse and addiction did not warrant listing in the Adverse Event “Table 8.”²⁰⁷ In other words, it was not a variable the authors were measuring, as corroborated by the absence of any instrument to assess addiction, despite the use of other survey questionnaires used to track other adverse events. Yet the authors claimed “Addiction was not reported as an adverse event for any participant.”²⁰⁸ The authors further stated “No cases of addiction were reported as an adverse event; this is in line with other studies, which have shown that opioids can be used in chronic noncancer pain without significant risk of abuse. [citing Jamison et al, Spine 1998].”²⁰⁹ The authors’ conclusions are not reliable based on methodology inadequacies to assess for addiction risk.

²⁰³ *Id.* at p. 1.

²⁰⁴ Portenoy, *et al.*, Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. Clin. J. Pain 2007; 23: 287-299.

²⁰⁵ Allan L, Richarz U, Simpson K, Slappendel R. Transdermal Fentanyl Versus Sustained Release Oral Morphine in Strong-Opioid Naive Patients With Chronic Low Back Pain. 2005;30(22):2484-2490, at p. 2484.

²⁰⁶ *Id.* at p. 2485.

²⁰⁷ *Id.* at p. 2488.

²⁰⁸ *Id.*

²⁰⁹ *Id.* at p 2489.

Even when investigators are attempting to detect addiction and abuse, as in the studies described above, the difficulties are daunting, as indicated by reports of patient concealment of problem behaviors and substantial disparities between questionnaire responses and urine drug screening; when researchers do not look for addiction and abuse, they are quite unlikely to find such evidence. Further, the study was underwritten by Janssen pharmaceuticals, the makers of Duragesic, transdermal fentanyl, suggesting bias conferred by industry sponsorship.²¹⁰

- B. Anderson *et al.* followed 30 patients prospectively for 24 months to assess the long-term safety and efficacy of chronic intrathecal morphine (injected into the spinal canal, or into the subarachnoid space so that it reaches the cerebrospinal fluid) in the treatment of chronic pain.²¹¹ Patients with “psychopathological or substance abuse problems” were screened out and deemed ineligible. Questionnaires were used to track many different variables, but none asked about signs and symptoms of opioid use disorder. The authors report that one patient (1/30, 3%) “was withdrawn from therapy because of drug-seeking behavior”²¹² This patient “complained of continually escalating pain after infusion system implant, despite successful pain relief during trial at an epidural dose of less than 10mg per day ... and sought to obtain oral narcotics from other health care providers,” although the authors do not disclose how they obtained this information. When further requests for dose increases were denied, the patient dropped out of the study.²¹³ The authors conclude “In general, the incidence of addiction among patients with nonmalignant pain receiving chronic opioid is low,” but their findings are unreliable given methodological failures to assess addiction risk. The study was sponsored by Medtronic, Inc., the makers of the intrathecal pump.²¹⁴
- C. Hassenbusch, like Anderson, examined a case series of patients (22) with intrathecal opioid infusion pumps. In this

²¹⁰ *Id.* at p. 2484.

²¹¹ Anderson VC, Ph D, Burchiel KJ. Prospective Study of Long-term Intrathecal Morphine in the Management of Chronic Nonmalignant Pain. 1999;44(2), at p. 289.

²¹² *Id.* at p. 292.

²¹³ *Id.* at pp. 295-296.

²¹⁴ *Id.* at p. 299.

case, they followed patients for 5 years.²¹⁵ The same limitations described in the Anderson study apply here: patients with history of mental illness or addiction were excluded,²¹⁶ and there were no screening instruments or any other detection method to assess for opioid misuse or addiction. Yet the authors conclude “There was no occurrence of opioid dependence, either physical or psychological....”²¹⁷

- D. McIlwain *et al.* did a 52-week open label extension study of oxymorphone extended release (ER) in patients with moderate to severe chronic osteoarthritis related pain.²¹⁸ The study was sponsored by Endo Pharmaceuticals, the makers of the study drug.²¹⁹ The study did not use screening instruments or other detection methods for opioid misuse or addiction. Their Table 2 of adverse events did not include opioid misuse/addiction, despite including 11 other opioid-related adverse events.²²⁰ Despite the absence of any method for detecting or measuring addiction risk, the authors concluded, “No instances of drug addiction or abuse were recorded.”²²¹
- E. Milligan *et al.* studied 532 chronic noncancer pain patients (only 301 completed the trial) being treated with transdermal fentanyl for up to 12 months. They report “drug abuse/dependence” in less than 1% of their sample, but qualify this by saying, “none was considered definitely related to the treatment.”²²² Like the other studies included in the addiction risk assessment of the 2010 Cochrane review, this study was not designed to reliably assess addiction risk: patients with a history of substance abuse or psychiatric disorders were excluded, no screening or detection instruments for opioid misuse or addiction were

²¹⁵ Hassenbusch, S, Stanton-Hicks, M, Covington, *et al.* Long Term Intraspinal Infusions Of Opioids in the Treatment of Neuropathic Pain. *Journal of Pain and Symptom Management*. 1995;10:527-543, at p. 529.

²¹⁶ *Id.* at p. 528.

²¹⁷ *Id.* at p. 536.

²¹⁸ McIlwain H, Ahdieh H. Safety , Tolerability , and Effectiveness of Oxymorphone Extended Release for Moderate to Severe Osteoarthritis Pain A One-Year Study. *Am J Ther*. 2005;112:106-112, p. 106.

²¹⁹ *Id.* at p. 111.

²²⁰ *Id.* at p. 108.

²²¹ *Id.* at p. 109.

²²² Milligan K, Lanteri-minet M, Borchert K, *et al.* Evaluation of Long-term Efficacy and Safety of Transdermal Fentanyl in the Treatment of Chronic Noncancer Pain. 2001;2(4):197-204. doi:10.1054/jpai.2001.25352, at p. 197.

described.²²³ The authors report three cases of “drug abuse (2 moderate and 1 severe)”; two cases of “moderate physical drug dependence (as opposed to abuse)”; and “no reports of addiction.”²²⁴ Yet how these concepts were defined and the cases detected are not clarified. The study was supported by a grant from Janssen.²²⁵ Despite these serious flaws, the authors concluded, “There were no reports of addictive behavior in any of the patients during this long-term study. Because the fear of addiction is one of the reasons for the underuse of opioids in chronic noncancer pain, this study provides further evidence that these fears are unfounded.”²²⁶ This conclusion does not follow from the evidence.

- F. The study by Mystakidou recruited 529 patients into an open-label study of transdermal therapeutic system-fentanyl (TTS-F) for 28 days, followed by an open-label follow-up for a median of 10 months between 1996-2002.²²⁷ The first page of the article includes the copyright symbol for the American Pain Society, which had been funded substantially by opioid manufacturers; the authors do not disclose a corporate sponsor, but they cite to prior studies of Dellemijn and Allan that acknowledged participation by Janssen-Cilag, the manufacturer of Duragesic TTS-F, and the Janssen Research Foundation.²²⁸ A complete description of exclusion criteria was not provided; the authors stated only, “Exclusion criteria included a history of opioid abuse, surgery in the preceding 7 days or scheduled surgery, contraindications to opioids, and opioids use outside of the designated treatment regimen.”²²⁹ No information is provided as to what constituted “contraindications to opioids;” and the exclusion for “opioids use outside the designated treatment regimen” inherently eliminates the population with the most obvious defining characteristic of addiction. The authors state, “Following discontinuation from the study, no patient complained of withdrawal symptoms or was

²²³ *Id.* at p. 198.

²²⁴ *Id.* at pp. 201-202.

²²⁵ *Id.* at p. 197.

²²⁶ *Id.* at p. 203.

²²⁷ Mystakidou, Kyriaki, Parpa, Efi, Tsilika, Eleni, Mavromati A, Smyrniotis V, Georgaki, Stavroula, Vlahos L. Long-Term Management of Noncancer Pain With Transdermal Therapeutic System-Fentanyl. *J Pain.* 2003;4(6):298-306. doi:10.1016/S1526-5900(03)00632-1, at pp. 298-299.

²²⁸ *Id.* at p. 305.

²²⁹ *Id.* at p. 299

found to display dependency”²³⁰; however, like the others described above, the Mystakidou study included no protocol to detect addiction, withdrawal, dependency or abuse, either during the study or after discontinuation. Without such information, it is unknown whether patients experienced such effects during the study, nor whether they returned to their former opioid regimens after the study ended.

- G. Portenoy describes an open label continuation study using controlled release (CR) oxycodone (Oxycontin) in a population of chronic pain patients who had previously participated in controlled trials of CR oxycodone for pain. Unlike the other studies included in the 2010 Cochrane review, this study by Portenoy *et al.* included specific methods for assessing opioid misuse and addiction, including an independent review panel to determine types of problematic opioid use. However, the information evaluated by the independent review panel was based entirely on patient self-report, which we know to be inherently unreliable, particularly in the context of a clinical trial designed to assess pain efficacy. The authors reported “6 of 227 (2.6%) patients could be considered to have probable drug abuse or dependence based on the independent expert review, none of whom met diagnostic criteria for substance abuse.”²³¹ This appears to be the basis for the “3%” figure used in the Noble 2010 review. However, the article also reported that 133 patients dropped out of the study, so the use of 227 as the denominator is questionable. Further, “Patients with self-reported past or present substance or alcohol abuse” were excluded, as were patients with a “documented allergy to oxycodone or other opioids.”²³² Finally, the study was sponsored by Purdue Pharma, the makers of Oxycontin.²³³
- H. Zenz described 100 chronic nonmalignant pain patients who were given opioids in an open-label, non-controlled setting, between 1986-1990.²³⁴ Treatment was discontinued in 59 patients (21 did not respond to opioid therapy; 20 changed to an alternative treatment method; 10 were

²³⁰ *Id.* at pp. 300-301.

²³¹ Portenoy, *et al.*, “Long Term Use,” fn. 204, above, at p. 296.

²³² *Id.* at p. 288.

²³³ *Id.* at p. 287.

²³⁴ Zenz, Michael; Strumpf, Michael; Tryba M. Long Term Oral Opioid Therapy in Patients with Chronic Nonmalignant Pain. 1992:69-77, at p. 70.

discontinued for “lack of compliance,” and 8 died during the study period).²³⁵ Zenz reported, “There were no cases of respiratory distress or addiction to opioids.”²³⁶ As in the studies described above, Zenz had no protocol to look for or record addiction or abuse. No details were provided as to the type of “noncompliance” that caused 10 patients to be discontinued, but “noncompliance” in the setting of opioid therapy is a red flag for concern over signs of abuse as to which the lack of further information is another conspicuous weakness of the study.

- I. In summary, the seven studies contributing to the addiction rate reported in the 2010 Cochrane review are subject to common inadequacies, primary among them their focus on efficacy and from lack of any method to detect addiction or abuse, and the screening out of higher risk patients. Their data do not square with the much higher prevalence of OUD reported among real world chronic pain populations, by investigators who were looking for it.
- j. Opioid manufacturers conveyed the misleading message that as long as doctors were prescribing opioids to patients in pain, the prescription pad conferred protection against patients becoming addicted. The false claim of low rates of addiction with prescription opioids when prescribed for pain had a significant impact on the increased likelihood that physicians would prescribe. Defendants successfully encouraged doctors into believing the risks of addiction were low, which directly contributed to increased prescribing, by promoting poor quality evidence highlighting low addiction rates among pain patients. Contrary to what Defendants claimed, opioid painkillers are as addictive as heroin purchased on a street corner, even when being prescribed by a doctor for a legitimate pain condition, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain.
- i. As mentioned above, the 1980 New England Journal of Medicine letter to the editor entitled “Addiction Rare in Patients Treated with Narcotics,” reported only four cases of addiction among 11,882 patients treated with opioids.²³⁷ This letter did not represent relevant or reliable evidence of the risk of opioids for chronic non-cancer pain, because the article pertained to a hospitalized population, including patients who received no more than a single dose, rather than the outpatient chronic pain population for whom opioid use was promoted and became prevalent.

²³⁵ *Id.* at p. 73.

²³⁶ *Id.* at p. 69.

²³⁷ Porter, Jick, *et al.*, “Addiction Rare,” fn. 39, above, at p. 123.

- ii. Nonetheless, it was widely cited by doctors and medical organizations and frequently quoted by the pharmaceutical industry in its advertisements for opioids in the treatment of chronic pain, as proving that “less-than-1%” of patients receiving opioids for pain becomes addicted.
- iii. Defendants’ promotional messages continued to cite their “less-than-1%” claim, or that addiction with chronic opioid therapy was “rare,” despite numerous peer-reviewed studies to the contrary over a period of decades. (See Appendix I.)
- iv. In 1992, Fishbain had published an earlier study of addiction risk with chronic opioid exposure, which stated, “According to the results of this review, to date, only three studies have attempted to address the concepts of psychological dependence and compulsive use, i.e., addiction, in an acceptable fashion. These studies have found a prevalence from 3.2% to a high of 16% for the possibility of addiction in chronic pain patients”.²³⁸ The same article also stated, “It is interesting to note that the only two studies to utilize urine toxicologies found illicit drug use in 6.41 and 12.5% of their chronic pain patients. These results may therefore indirectly support the results of the other ‘addiction’ studies described earlier, as they are both within the prevalence percentages derived from these studies”.²³⁹ However, these higher prevalence figures, and the sources from which they came, were omitted from Fishbain’s 2008 analysis.
- v. Also, Fishbain’s 2008 review²⁴⁰ included data from a 1992 study by Bouckoms, *et al.*, which found that 14 of 59 clinic patients (24%) taking opioids for long-term met criteria for “narcotics addiction”.²⁴¹ Bouckoms also stated: “The influence of population sample bias in prevalence studies of narcotic addiction is dramatically shown in a comparison of studies in the literature. Table 5 summarizes data from the studies of Porter, Maruta, Taub, Evans, Langemark, and Portenoy, wherein the prevalence of addiction was 0.03%, 24%, 4.2%, 7%, 35%, and 5%, respectively”.²⁴² Notably, the 0.03% figure in Bouckoms’ text is based on the Porter and Jick 1980 Letter²⁴³—the only one of the 5

²³⁸ Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain*. 1992. doi:10.1097/00002508-199206000-00003, at p. 80.

²³⁹ *Id.* at p. 81.

²⁴⁰ Fishbain, *et al.*, “What Percentage,” fn. 177, above.

²⁴¹ Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. *Ann Clin Psychiatry*. 1992. doi:10.3109/10401239209149570, at p. 185.

²⁴² *Id.* at p. 188.

²⁴³ Porter, Jick, *et al.*, “Addiction Rare,” fn. 39, above, at p. 123.

references that was *not* based on a population of patients treated with opioids for chronic pain.

- vi. All of the sources cited by Bouckoms were available to Defendants from 1992 on. Yet their marketing and promotional statements beginning in the 1990s cited the inapt Porter and Jick study²⁴⁴ of hospitalized patients with any exposure to opioids, regardless of duration, as the source for the claim of “less than one percent” prevalence of addiction. I am not aware of any Defendants having issued a marketing or promotional statement citing the results of 24%, 4.2%, 7%, 35% or 5%, referenced by Bouckoms in 1992.²⁴⁵ Nor am I aware of any such statements by Defendants that cited the range of “prevalence from 3.2% to a high of 16% for the possibility of addiction” reported by Fishbain in 1992.²⁴⁶
- vii. Later publications also reported addiction rates that did not appear in the promotional materials that I have reviewed. These include the following prevalence studies cited in the Vowles²⁴⁷ data synthesis: Manchikanti (2003),²⁴⁸ Cowan (2003),²⁴⁹ Adams (2006),²⁵⁰ Fleming (2007),²⁵¹ Banta-Greene (2009),²⁵² Schneider (2009),²⁵³ Edlund (2007),²⁵⁴ Højsted (2010),²⁵⁵ Jamison (2010),²⁵⁶

²⁴⁴ *Id.*

²⁴⁵ Bouckoms, *et al.*, “Chronic Nonmalignant,” fn. 241, above, at p. 188.

²⁴⁶ Fishbain, *et al.*, “Drug Abuse,” fn. 238, above, at p. 80.

²⁴⁷ Vowles, *et al.*, “Rates of Opioid Misuse,” fn. 153, above.

²⁴⁸ Manchikanti et.al Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *J Ky Med Assoc* 2003;101:511–17, at p. 511.

²⁴⁹ Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. *Pain Med.* 2003;4(4):340-351, at p. 340.

²⁵⁰ Adams EH, Breiner S, Cicero TJ, *et al.* A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain. *J Pain Symptom Manage.* 2006;31(5):465-476, at p. 465.

²⁵¹ Fleming, *et al.*, “Substance Use Disorders,” fn. 151, above, at p. 573.

²⁵² Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn D a. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug Alcohol Depend.* 2009;104(1-2):34-42, at p. 37.

²⁵³ Schneider, MD, PhD JP, Kirsh, PhD KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. *J Opioid Manag.* 2010;6(6):385-395, at p. 390.

²⁵⁴ Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med.* 2007. doi:10.1111/j.1526-4637.2006.00200.x, at p. 651.

²⁵⁵ Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain.* 2010;14(10):1014-1020, at p. 1014.

²⁵⁶ Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender Differences in Risk Factors for Aberrant Prescription Opioid Use. *J Pain.* 2010. doi:10.1016/j.jpain.2009.07.016, at p. 5.

Passik (2011),²⁵⁷ and Meltzer (2012),²⁵⁸ which reported addiction at 8.4%, 2.8%, 4.9%, 3.8%, 13%, 15.7%, 0.7%, 14.4-19.3%, 34.1%, 6-11%, and 23%, respectively.

- viii. With one exception, all of these studies showed addiction prevalence multiple times higher than the “less than one percent” figure that Defendants continued to cite, while omitting data from these peer-reviewed studies of relevant, real world populations of chronic opioid patients.
- ix. The sole exception, the Edlund (2007) study, can be explained in that the 0.7% incidence pertained to the entire healthcare database, rather than the subset of prescription opioid users. As to the latter group, the incidence of addiction was actually 7.3%,²⁵⁹ which is consistent with the other data synthesized by Vowles. Because this distinction is important and not obvious, I provide the additional details below.
 - A. First, the data used in the Edlund 2007 study came from a nationally representative community sample, Healthcare for Communities (HCC). The sample consisted of 9,279 people who were interviewed to investigate self-reported opioid misuse and “problem” opioid misuse among users and non-users of prescribed opioids, as well as use/ “problem use” of other substances (illicit drugs other than opioids, alcohol). “Opioid misuse” was defined to mean either without a doctor’s prescription, or in a larger amount or for a longer time than prescribed. “Problem opioid use” added criteria of tolerance and/or psychological or emotional problems due to drug use to the general “misuse” definition.²⁶⁰
 - B. This Edlund study did not provide any data on “addiction.” Nevertheless, the Vowles data synthesis included a value of 0.7% for “addiction.”²⁶¹ However, the Edlund definition of “problem opioid use” is consistent with Vowles’ definition of “addiction” to mean a “[p]attern of continued use with experience of, or demonstrated potential for, harm, (e.g.,

²⁵⁷ Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *J Pain Symptom Manage*. 2011;41(1):116-125, at p. 116.

²⁵⁸ Meltzer, E, Rybin, D, *et al.* Aberrant Drug-Related Behaviors: Unsystematic Documentation Does Not Identify Prescription Drug Use Disorder. *Pain Med*. 2012 November; 13(11): 1436-1443, at 1437.

²⁵⁹ Edlund, *et al.*, “Do Users Have Higher Rates,” fn 254, above, at p. 651.

²⁶⁰ *Id.* at pp. 649-650.

²⁶¹ Vowles, *et al.*, “Rates of Opioid Misuse,” fn. 153, above, at p. 572, Table 2.

impaired control over drug use, compulsive use, continued use despite harm, and craving).”²⁶²

- C. Further, the reference to “0.7%” in the Edlund 2007 article appearing at p. 651, stated the percentage of problem opioid misuse in “*the total HCC sample*,” (emphasis added), which consisted of 8,997 (97%) nonusers of prescription opioids compared to 282 (3%) of the HCC sample who were prescription opioid users. The Edlund study reported, “Rates of problem opioid misuse were *significantly higher in those with prescription opioid use* (7.3%, 17 out of 282, vs. 0.5%, 69 out of 8,997, $P < 0.001$.”; emphasis added).²⁶³
- D. In the absence of any data specific to addiction in the Edlund article, it can only be inferred that Vowles intended to use Edlund’s “problem opioid misuse” as a surrogate for addiction, and that the reference to 0.7% for the total population is inappropriate, since all of the other studies that Vowles synthesized had determined the percentage of addiction/ misuse among subjects exposed to prescription opioids, and not the percentage of addiction/misuse among a general population consisting almost entirely of non-users of prescription opioids.
- E. Thus, the proper figure from the Edlund study to include in the Vowles data synthesis would have been “7.3%, 17 out of 282” prescription opioid users, and the inclusion of the prescription opioid nonusers differentiates the Edlund study from all others that Vowles used in his data synthesis. At 7.3%, the Edlund study is very similar to the range of 8-12% addiction that Vowles assessed for the studies as a whole.
- F. Finally, Edlund acknowledged, “Our analyses of substance abuse rely on self-report, which might suffer from recall bias, or respondents might under-report symptoms due to the stigma associated with illicit substance abuse. To the extent this is true, our results are underestimates of the true rates.”²⁶⁴ Accordingly, 7.3% is a lower bound, and the true rate of addiction among the population in the Edlund study may well have been greater.

²⁶² *Id.* at p. 570.

²⁶³ Edlund, *et al.*, “Do Users Have Higher Rates,” fn. 254, at p. 651.

²⁶⁴ *Id.* at p. 654.

- x. Purdue’s Power Point presentation dated September 12, 2014, is addressed to a potential business opportunity involving “Project Tango.” The document identifies Tango as the “global leader in the pharmaceutical treatment of addiction,” and further states, “Addiction treatment is a good fit and natural next step for Purdue,” because “Pain treatment and addiction are naturally linked.”²⁶⁵ I agree that pain treatment with opioids is naturally linked with addiction. Furthermore, this linkage would have been known and obvious to Defendants throughout the period of time when they marketed and promoted their opioid medications with the false message that addiction was “less than 1%,” or “rare,” or “uncommon,” and that false message deprived doctors and patients of necessary data to inform the true risks of chronic opioid therapy.

6. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate claims as to the levels to which doses can be safely increased. With increasing dosage and duration of opioids, the risk of addiction goes up, as do the risks of many other adverse health consequences, including tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, severe constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, accidental overdose, and death. There is an undeniable link between suicide and opioids. Opioids are associated with more adverse medical outcomes and more mortality than non-opioid analgesics (NSAIDS).

- a. Through drug reps, key opinion leaders, and CME content, manufacturers of opioids conveyed the misleading message that there is no ceiling dose for opioids. In an article by Portenoy’s 1986 co-author Foley and others they wrote “We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect.”²⁶⁶ This statement encouraged the practice of increasing the dose of opioids over time as tolerance developed. I have seen scores of patients over the years on very high doses of opioids, some as high as 2,000 morphine milligram equivalents per day (MED). To put that in perspective, the average heroin addicted individual consumes 100 morphine milligram equivalents daily. Meanwhile, there is no evidence to support the use of higher doses of opioids, and mounting evidence that risks of opioids are directly related to dose and duration: the higher the dose, and the longer patients are on them, the higher the risk.²⁶⁷
- b. A study by Dunn *et al.* found an increased risk of opioid-related overdose death in a step-wise dose response relationship: “Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients

²⁶⁵ PPLPC016000255303, produced natively at *14 and *8.

²⁶⁶ Foley KM, Fins JJ, Inturrisi CE. A true believer’s flawed analysis. *Arch Intern Med.* 2011. doi:10.1001/archinternmed.2011.166, at p. 867.

²⁶⁷ Edlund, *et al.*, “Role of Opioid Prescription,” fn. 25, above, at p. 557.

receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. ... Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients.”²⁶⁸

- c. Dunn also noted that their study “provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses.”²⁶⁹ The study also provided important data on the relationship between fatal and non-fatal overdoses, in particular, that “[m]ore than 7 nonfatal overdoses events occurred for each fatal overdose” in the study cohort.²⁷⁰ ... “The inclusion of nonfatal overdoses improves understanding of the problem, because most previous work has examined only fatal overdoses. The overall overdose rate in the sample was 148 per 100,000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious.”²⁷¹ These data mean that on a nationwide basis, the over 14,000 fatal prescription opioid overdoses in 2017 would translate to over 100,000 nonfatal overdoses. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, to treat the overdose episode itself, and to provide long-term care for the OUD disease that gave rise to the event.
- d. A study by Bohnert *et al.* found an increased risk of opioid-related overdose death at each level of increased dose, and particularly at doses greater than 100 MEDs. Compared to the Reference dose of 1 to < 20 MED, the adjusted hazard ratio for 20 to < 50 MED was 1.88; for 50 to < 100 MED, the hazard ratio was 4.63; and at > 100 MED, the hazard ratio was 7.18; all three results were statistically significant. A similar pattern held for each of three diagnostic groups (substance use disorders, chronic pain, and cancer): “The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR = 4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA] = 0.14%); among those with chronic pain, adjusted HR = 7.18 (95% CI, 4.85-10.65; ARDA = 0.25%); among those with acute pain, adjusted HR =

²⁶⁸ Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med.* 2010;152(2):85-92, at p. 85.

²⁶⁹ *Id.* at p. 90.

²⁷⁰ *Id.* at p. 89.

²⁷¹ *Id.* at p. 91.

6.64 (95% CI, 3.31-13.31; ARDA = 0.23%); and among those with cancer, adjusted HR = 11.99 (95% CI, 4.42-32.56; ARDA = 0.45%).”¹⁰⁹²⁷² Opioid therapy is generally accepted as appropriate for cancer patients, especially in late stages or severe pain. Nevertheless, with the advent of improved cancer therapies, more patients are living longer with disease or remission, and opioid therapy should be implemented with caution, to minimize risk of addiction.

- e. A population based nested case control study of 607,156 people prescribed opioids found that an average daily dose of 200 mg or more of morphine or equivalent was associated with a nearly 3-fold, statistically significant increased risk of opioid-related mortality relative to low daily doses (< 20 mg of morphine or equivalent), Odds Ratio (OR) 2.88, 95% CI 1.79-4.63.²⁷³
- f. The risk of addiction, like the risk of overdose and mortality, also increases in a dose-dependent manner. As previously stated, “Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially.”²⁷⁴ For low dose (1-36 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).²⁷⁵
- g. The link between suicide and opioids is undeniable and complex. In a *New England Journal of Medicine* article on opioids and suicide risk, Bohnert *et al.* note that “A reduction in the quantity of prescribed opioids may function as a ‘means restriction’ by reducing patients’ access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients’ access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity.

²⁷² Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc.* 2011;305(13):1315-1321, at p. 1315; Olsen, *et al.*, Pain relief that matters, fn 107, above.

²⁷³ Gomes *et.al.*, “Opioid Dose,” fn. 124, above, at p. 686.

²⁷⁴ Edlund, *et.al.* “Role of Opioid Prescription,” fn. 25, above, at p. 561.

²⁷⁵ *Id.* at pp. 559-560.

However, whether tapering changes the risk of either suicide or overdose is unknown.”²⁷⁶

- h. Opioids are associated with more adverse medical outcomes and increased mortality than non-opioid analgesics (NSAIDs),²⁷⁷ contrary to the claim that morbidity and mortality of non-opioid medications (NSAIDs) for pain are comparable.²⁷⁸

7. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including mischaracterizing addictive behavior as “pseudoaddiction” and tolerance as “breakthrough pain.” There is no such thing as “pseudoaddiction,” and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.

- a. Tolerance is the need for more and more of the drug to get the same effect. As the dose is increased to overcome tolerance to the pain relieving effects of the drug, patients are exposed to the other dose-dependent risks associated with the drugs, including the risk of death. Furthermore, tolerance to the respiratory suppressant effects (the ability of opioids to decrease breathing rate and thus blood oxygenation) develops more slowly than tolerance to the pain-relieving effects of the drug. As such, as the dose of opioids goes up to target pain relief, the breathing rate goes down, increasing the risk of accidental overdose and death.²⁷⁹ Tolerance is not a short-lived phenomenon. It persists and renders the opioid largely ineffective for the underlying pain condition. Despite tolerance, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose.
- b. Based on a single case report of a patient who engaged in drug-seeking behavior,²⁸⁰ doctors were encouraged to conceptualize the patient’s addictive behavior as evidence of under-treated pain. This case report was co-authored by David Haddox, who went on to work at Purdue. The

²⁷⁶ Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 76

²⁷⁷ Solomon DH, Rassen J a, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010;170(22):1968-1976. doi:10.1001/archinternmed.2010.391, at p. 1968.

²⁷⁸ Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, nonopioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.

²⁷⁹ Lembke, *et al.*, “Weighing the Risks,” fn. 3, above, at p. 987; Chou, *et al.*, “Effectiveness and Risks,” fn. 60, above, at p. ES-25.

²⁸⁰ Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989;36(3):363-366. <http://www.ncbi.nlm.nih.gov/pubmed/2710565>.

authors of the case report incorrectly asserted that treatment of pain is often inadequate because of “excessive fears of tolerance and dependence by both health professionals and the public,”²⁸¹ when in fact those fears were well-justified and should have been respected. In addition, since the conditions of addiction and dependence are common, their recommended treatment to continue administering or even increase opioids despite addictive behavior, undoubtedly put more patients at risk of becoming addicted or dependent.

- c. Patients develop tolerance over time to daily opioids, such that the opioid partially or completely stops working to relieve pain. Once tolerance occurs, patients may experience opioid withdrawal multiple times a day between pain pill doses, and need higher and higher doses to avoid between-pill withdrawal. Tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication. Instead, in the 1990’s and early aughts, Defendants’ promotional messages advised doctors that drug-seeking behavior should be considered “pseudoaddiction,” that should be addressed by increasing opioids or ‘rotating’ to another opioid to manage tolerance, which in turn led to patients being escalated to higher doses that conferred greater risk. (See Appendix for examples).
- d. In a review article on use of the term ‘pseudoaddiction,’ the authors found, “By 2014, pseudoaddiction was discussed in 224 articles. Only 18 of these articles contributed to or questioned pseudoaddiction from an anecdotal or theoretical standpoint, and none empirically tested or confirmed its existence. Twelve of these articles, including all four that acknowledged pharmaceutical funding, were proponents of pseudoaddiction In contrast, six articles, none with pharmaceutical support, questioned pseudoaddiction as a clinical construct.”²⁸² Further, the authors wrote, “In conclusion, we find no empirical evidence yet exists to justify a clinical ‘diagnosis’ of pseudoaddiction.”²⁸³ I agree that there is no empirical evidence to justify a diagnosis of pseudoaddiction, and that use of this term was spread by the manufacturers of prescription opioids, with the explicit and dangerous message to doctors that more opioids should be prescribed.
- e. To “correctly define addiction” the PPSG took consensus definitions from the American Society of Addiction Medicine, American Academy of Pain Medicine, and the American Pain Society.²⁸⁴ Those included a definition

²⁸¹ *Id.* at p. 365.

²⁸² Greene MS, Chambers RA. Pseudoaddiction : Fact or Fiction ? An Investigation of the Medical Literature. 2015:310-317. doi:10.1007/s40429-015-0074-7, at p. 310.

²⁸³ *Id.* at p. 314.

²⁸⁴ WIS_PPSG_002042, June 8, 2001.

of the term “pseudoaddiction: “Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may “clock watch,” and may otherwise seem inappropriately “drug seeking.” Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.”²⁸⁵ Thus, PPSG, an entity funded by the Pharmaceutical Opioid Industry, aligned with and promoted the Industry-supported view of “pseudoaddiction” as a real diagnosis for which more opioids were the prescribed treatment. (See Appendix II to this report).

8. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including characterizing opioid dependence as a benign state that is easily reversible. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Once established, opioid dependence represents a complex, debilitating, and sometime irreversible clinical problem. In most cases, these patients require a protracted medically supervised taper to lower their doses. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.

- a. Opioids cause neuroadaptation²⁸⁶ and lead to tolerance, physiologic dependence, and painful withdrawal, even without the more complex biopsychosocial disease of addiction. As such, tolerance, dependence, and withdrawal in and of themselves represent real harm to patients as a result of opioid therapy. Due to tolerance, dependence, and withdrawal, many patients taking prescription opioids today will require an enormous investment of resources to help them get off of opioids or onto lower, safer doses. (See section on “Ending the epidemic” for a fuller description of what is required to help this population.)
- b. Physiologic dependence, as currently defined by the DSM-5, is not the same as addiction. Dependence is the process whereby the body comes to rely on the drug to maintain biochemical equilibrium. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as the signs and symptoms of withdrawal. Although opioid dependence as currently defined is not the same as addiction, dependence on opioids can be associated with significant morbidity and mortality, and thus is not the same thing as dependence on other medications used as evidence-based treatment for

²⁸⁵ *Id.*

²⁸⁶ Koob, *et al.*, “Neurocircuitry,” fn. 14, above, at p. 557.

illness.²⁸⁷ Also, while dependence is defined differently from addiction, the line between them is not well-defined; in particular, the evidence of addiction often comes when an opioid-dependent patient attempts to taper and discovers that the loss of the drug causes the craving and compulsion that define addiction. In my clinical experience, dependence in some individuals can develop quickly. This clinical experience is consistent with studies showing that even short-term prescriptions of opioids for acute injuries result in long-term use of opioids after the acute condition has passed.²⁸⁸ In the DSM-4, the edition prior to the DSM-5, “opioid use disorder” was called “opioid dependence.” The new DSM-5 criteria made it more difficult to diagnose Opioid Use Disorder (opioid addiction), by removing the criteria of withdrawal, and tolerance from the definition in the case of a patient taking prescribed opioids under a doctor’s care. The DSM-5 thereby reduced the proportion of patients who could be diagnosed with opioid use disorder.

- c. On May 18, 2006, Purdue’s David Haddox received the “excellent news” from Sidney Scholl, of Pinney Associates, that “Chuck O’Brien will be heading up the SUD [Substance Use Disorder] section of the DSM-V. This means that there is a good chance that ‘addiction’ will replace ‘dependence’ and there can be some changes in the diagnostic criteria that will reflect issues related to abuse and addiction of prescription opioids. Chuck asked me to assist him in this process. I would appreciate your input in this process. ... If Marc Schuckit, who was originally slated to head up the SUD section, was still in charge, we would not be in this position as he likes the use of dependence over addiction. This is an opportunity we should not overlook, as major revisions of the DSM do not occur very often.” Haddox wrote back, “This is really good news, Sid.”²⁸⁹
- d. On March 24, 2008, Haddox wrote to Phillipp Lippe in response to Lippe’s request for comments regarding the American Medical Association’s Report on Substance Abuse. Haddox wrote, “I am glad to see AMA getting into this area. Certainly the definitions and diagnostic criteria need some work...we are all fortunate that Charles O’Brien is the head of the substance use disorders section.”²⁹⁰
- e. On November 6, 2008, Haddox wrote to Chuck O’Brien, “It was good to see you this past weekend at ICPCD [International Conference on Pain and Chemical Dependency]. I really am excited that you are educating your nonclinical colleagues about the need for diagnostic nomenclature

²⁸⁷ Lembke, *et al.*, “Weighing the Risks,” fn. 3, above.

²⁸⁸ Delgado M, Al. K et. National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naïve Patients Treated in the Emergency Department for Ankle Sprains. *Ann Emerg Med.* 2018, at p. 1; see also Howard, *et al.*, “Association of Prescribing,” fn. 125, above, at p. E-6.

²⁸⁹ PPLP004058443.

²⁹⁰ PPLPC031000425439.

that are applicable in the real (read:clinical) world.” Haddox went on to ask O’Brien to consult on a tamper-resistant opioid analgesic work group, and referenced prior payment of \$2400 at O’Brien’s rate of \$600 per hour, “when it was anticipated that you would accompany us to the FDA Advisory Committee in March.” Haddox added, “Also, in the interest of public health and medicine, I don’t want to do anything to impair your ability to complete your DSM-V duties.” O’Brien wrote back on November 12, 2008, to “Dave, I would be very happy to do this but it would simplify my life with Penn if we could considered this activity an extension [of] my efforts of several months ago where I already signed a contract.” Haddox replied to that he was “really pleased that you will be able to work with us on this.”²⁹¹

- f. On March 25, 2008, Haddox again exchanged emails with Phillipp Lippe. Dr. Lippe expressed concern that under DSM-IV, the first three criteria for diagnosis of substance dependence “are inherent in pain management,” that is, “(1. Tolerance; (2) withdrawal symptoms; and (3) increased dosage or length of use.” Haddox wrote to Lippe, “I have great confidence that the DSM-V will improve on this language, based on the chair of the SUD [committee].”²⁹²
- g. This sequence of events indicates that Purdue’s consultant, O’Brien, who was on a first name basis with Haddox, was responsible for the work that altered the DSM-V definition of opioid use disorder in a manner that suited Purdue’s goals by distinguishing between “dependence” on the one hand, and “use disorder” or “addiction” on the other. This history is consistent with a larger effort on the part of Purdue to characterize dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance, are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena.
- h. Ohio statutory definition of “Drug dependent person” means “any person who, by reason of the use of any drug of abuse, is physically, psychologically, or physically and psychologically dependent upon the use of such drug, to the detriment of the person’s health or welfare.”²⁹³ Like the DSM-5, the Ohio definition makes a distinction between “physically” and “psychologically” dependent, and includes both of these phenomena as types of harm. In other words, according to Ohio law, the “drug dependent person” includes both persons with opioid use disorder/addiction (DSM-5 definition) and persons who are physically dependent on opioids, even if not addicted. I would agree with this definition.

²⁹¹ PPLPC018000252189, at pp. 190-191.

²⁹² PPLPC018000201219, at pp. 1219-1222.

²⁹³ Ohio Revised Code §3719-011.

- i. Regardless of these changing and disparate definitions, the bottom line has not changed: prescription opioids induce physiological dependence almost universally, and result in addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Both represent significant harms.
- j. Even limited exposure to opioids through a doctor's prescription, can lead to persistent opioid use. In other words, once patients start opioids, they are at high risk to continue them beyond the time of injury.
 - i. Brummett *et al.* sought to determine the incidence of new persistent opioid use after minor and major surgical procedures. Using a nationwide insurance claims data set from 2013 to 2014, they calculated the incidence of persistent opioid use for more than 90 days among opioid-naïve patients after both minor and major surgical procedures. The authors found the rates of new persistent opioid use were similar between the two groups, ranging from 5.9% to 6.5%. By comparison, the incidence in the nonoperative control cohort was only 0.4%. The authors wrote, "New persistent opioid use represents a common but previously underappreciated surgical complication that warrants increased awareness."²⁹⁴ The more opioids prescribed after surgery, the more patients tend to use. The number of opioid pain pills prescribed after surgery is a bigger predictor of how many opioids the patient will use, than is self-reported pain.
 - ii. A study by Delgado *et al.* looked at opioid naïve patients being treated for a common minor injury, ankle sprain, in the emergency department (ED) to determine the association between initial opioid prescription intensity and transition to prolonged opioid use. The authors concluded that opioid prescribing for ED patients treated for ankle sprains is "common," and prescriptions greater than 225 MED were associated with approximately five times higher rates of prolonged opioid use than with lower MED exposure. As the authors stated, "This is concerning because these prescriptions could still fall within 5- or 7-day supply limit policies aimed at promoting safer opioid prescribing."²⁹⁵
- k. Clinical experience and clinical studies demonstrate that the majority of opioid legacy chronic pain patients (that is, patients who have been taking opioids daily for months to years) are physiologically dependent on opioids and struggle to taper, even when opioids pose imminent risk.

²⁹⁴ Brummett CM, Waljee JF, Goesling J, *et al.* New persistent opioid use after minor and major surgical procedures in us adults. *JAMA Surg.* 2017., at p. 1.

²⁹⁵ Delgado, *et al.*, "National Variation," fn. 288, above, at p. 1.

- i. Withdrawal refers to the physiologic manifestations of not having the substance, the symptoms of which vary from substance to substance. As a general albeit oversimplified principle, the characteristics of withdrawal from a given substance are the opposite of intoxication for that substance. Withdrawal from opioids includes dysphoria (unhappiness), anxiety, insomnia, agitation, restlessness, muscle fasciculations, increased heart rate, elevated blood pressure, diarrhea, nausea, vomiting, and body pain. In some cases, the suffering is so extreme that patients say they would rather die than go through it. Although opioid withdrawal is generally thought to be painful but not life threatening, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.²⁹⁶
- ii. In a study at Oregon Health & Sciences University, after a hospital and clinic wide policy was implemented to get high dose legacy patients' doses down below 120 MED per day, including intensive physician education from 2011 to 2013,²⁹⁷ 71 (63%) continued high-dose opioids in the post-intervention period.²⁹⁸ In other words, even with a hospital wide initiative, a minority of patients tapered to safer doses.
- iii. In a Danish study in which subjects were tapered off of opioids by reducing by 10% of the daily opioid dose every week until discontinuation,²⁹⁹ only 13 of 35 patients randomized to the opioid taper completed the study without dropping out. The authors wrote "Although our study is hampered by a vast dropout rate, we still feel that it is highly justified to point to the fact that the stabilization of opioid treatment is not a simple task and opioid tapering off seems to be extremely difficult in CNCP patients in general...."³⁰⁰
- l. Based on the literature and my own experience, I have worked with others to develop a protocol for safely and compassionately tapering opioid-dependent patients to lower doses or to eliminate them entirely. See discussion of the "BRAVO Protocol" below.

²⁹⁶ Stark MM, Payne-James J. People can die from opiate withdrawal. *Med Sci Law*. 2017;57(2):103. doi:10.1177/0025802417704600 at p. 103; see also Bohnert, *et al.*, "Association Between Prescribing Patterns," fn. 272, above, at p. 77.

²⁹⁷ Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016;37(1):141-147, at pp. 141-142.

²⁹⁸ *Id.* at p. 114.

²⁹⁹ Kurita GP, Højsted J, Sjøgren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *Eur J Pain*. 2018;22(8):1528-1543, at p. 1531.

³⁰⁰ *Id.* at p. 1536.

- m. Defendants’ promotional documents conveyed the message that prescription opioid dependence is not a significant concern, and that patients can be easily tapered off their prescriptions in a brief period of time. That message is contradicted by the scientific literature, my own experience, and patients’ own accounts.³⁰¹ This messaging improperly contributed to physicians’ false sense of security in the belief that prescription opioids can be prescribed without substantial risk. (See Appendix I). Further, misleading statements by Defendants on the efficacy of opioids in the treatment of chronic pain (see Appendix I), are challenged by the findings that pain improves in many chronic pain patients who are tapered down and/or off of opioids.

9. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.

- a. Over the course of the marketing of opioids for chronic pain, as the epidemic of addiction has grown, a number of physicians have attempted to develop “screening” instruments that might identify patients at high risk of addiction, who could then be screened out of opioid therapy, or closely monitored if such therapy were instituted. However, even if screening for established risk factors were implemented, data support the conclusion that OUDs would not be eliminated. In the Edlund study, the odds ratio for the incidence of OUDs associated with chronic use, even at low doses, was far higher than the odds ratio for established risk factors that screening instruments attempt to identify. In particular, the odd ratios with chronic low dose use (14.92), medium (28.69), and high dose (122.45) were all substantially greater than the odd ratios for mental health diagnosis (3.12); multiple mental health diagnoses (5.71); prior alcohol use disorder (3.22); and prior non-opioid abuse disorder (8.26).³⁰² For chronic/high dose opioid use, the odds ratio of approximately 122 is 40 times greater than for a mental health or alcohol use diagnosis, and 15 times higher than for a prior non-opioid use disorder. According to these data, the chronic use of opioids is responsible for far more OUDs than the existence of identifiable risk factors for OUDs.
- b. It is true that *a priori* risk of addiction is related to genetics (a biological parent or grandparent with addiction), as well as complex psychosocial

³⁰¹ Rieder TN. In opioid withdrawal, with no help in sight. *Health Aff.* 2017;36(1):182-185. doi:10.1377/HLTHAFF.2016.0347

³⁰² Edlund, *et al.*, “Role of Opioid Prescription,” fn. 25, above, at p. 563.

factors such as co-occurring mental illness, poverty, unemployment, multigenerational trauma, and peer influence. Persons with a history of addiction are more likely to develop problematic opioid use to the opioid their doctor is prescribing.³⁰³ These risk factors notwithstanding, it is also true that addiction can occur in persons with none of these risk factors, and it is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. Hence, caution and monitoring are necessary for all patients being prescribed these medications, and even then will never be a failsafe method.

- c. A validated screening instrument to predict which patients are more vulnerable to the adverse consequences of opioid therapy, including addiction, is theoretically of benefit, but to date, none has been shown to predict future adverse consequences. Kaye *et al.* summarizes the progress in a narrative review as follows: “Although several screening instruments and strategies have been introduced in recent years, there is no single test or instrument which can reliably and accurately predict those patients not suitable for opioid therapy or identify those who need increased vigilance or monitoring during therapy.”³⁰⁴
- d. Chou *et al.*, in reviewing four studies that evaluated the accuracy of risk assessment instruments, found that three studies reported “inconsistent results” for the 10-item Opioid Risk Tool No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse.”³⁰⁵
- e. Indeed the Opioid Risk Tool, which was touted by Defendants for screening patients who could ‘safely’ be prescribing opioids, has recently been invalidated. “In this population, we were not able to replicate the findings of the initial ORT study. Self-report was no better than chance in predicting those who would have an opioid aberrant behavior. The ORT risk variables did not predict aberrant behaviors in either gender group. There was significant disparity in the scores between self-reported ORT and the ORT supplemented with medical record data (enhanced ORT).”³⁰⁶
- f. There is a potential risk of any opioid risk tool: that prescribers gain a false sense of knowing who can and cannot get addicted, when in fact the biggest predictors of opioid dependency and addiction are access to opioids in the first place, and dose and duration, not personal characteristics. Indeed this focus on risky patients, rather than the inherent

³⁰³ Weisner CM, Campbell CI, Ray GT, *et al.* Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain*. 2009;145(3):287-293, p. 292.

³⁰⁴ Kaye A, Jones M, Kaye A, *et al.* No Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1. Title. *Pain Physician J.* 2017, at p. 573.

³⁰⁵ Chou, *et al.*, Effectiveness and Risks – Systemic,” fn. 60, above, at p. 280.

³⁰⁶ Clark, *et al.*, “Re-assessing the Validity of ORT,” fn. 144, above, at p. 1382.

risk associated with opioids themselves, has been the prevailing thinking in the 1980's, 1990's, and 2000's, encouraged by the Defendants' promotional messages, and is in part responsible for the opioid epidemic we face today. Prescribers were incorrectly taught that by screening out high risk patients, they would avoid opioid misuse and addiction.

- g. Further, because of Defendants' aggressive promotion of the great benefits and minimal risks of prescribing opioids for pain, it would have been reasonable for doctors to conclude that there was little or no need for screening.
- h. Finally, it is unlikely that asking patients about risk factors will ever be a suitable method of screening, as motivation to minimize or omit risk factors in pursuit of obtaining a specific type of drug will weigh heavily on the truthfulness and transparency of reporting (See discussion of Fleming study, above).

10. In sum, the Pharmaceutical Opioid Industry made misleading marketing claims to promote the above misconceptions, in the absence of reliable scientific evidence. Taken together, these misconceptions were the single most significant factor giving rise to the massive increase in the sale of opioids and the resulting epidemic of dependence and addiction, as detailed in this Report. Further, the actions of the Pharmaceutical Opioid Industry significantly influenced doctors and others who made decisions that increased the population's exposure to prescription opioids. Other developed countries with similar populations that experience chronic pain, but which have not had the same aggressive marketing as in the U.S., have not experienced any comparable degrees of prescription opioid overuse, mortality, and morbidity, supporting the conclusion that the marketing is the factor that made the difference.

- a. To understand how insidious, pervasive, and misleading the opioid marketing was (and continues to be to this day), it is relevant to examine a published peer reviewed article in the medical literature on pain and opioids, dissect the misleading science contained therein, trace the affiliation of its authors back to opioid manufacturers, and uncover how a 'scientific article' was then used by opioid manufacturers as promotional material. In other words, peer reviewed articles written by key opinion leaders and/or sponsored by the Defendants, were disseminated to prescribers under the guise of science, when in fact they represented marketing tools. To illustrate, an example is provided below.
 - i. A report by Endo Pharmaceuticals created for its sales representatives included reference to an article by Katz et al, "A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid naive

patients with chronic low back pain.”³⁰⁷ This article was cited as support for “Key Feature Messages” in the Endo document providing “suggested approach for call planning.”³⁰⁸

- A. The Katz study included Endo employees as authors and was Endo sponsored.³⁰⁹
- B. In the “Key Features Messages” used to train Endo’s sales staff, one of the claim messages they were instructed to convey, ostensibly based on the Katz article, was that over 70% of patients on oxymorphone extended release (Opana ER) achieved greater than 50% pain relief. .”³¹⁰ In reality, this is a misleading figure for the reasons below.
- C. The “>70%” figure, who purportedly achieved > 50% pain reduction, was based on only the fraction of patients randomized to Opana who were able to complete the randomized controlled trial. In reality, 325 patients were recruited for the open label “enriched enrollment” phase which exposed all 325 to Opana, and 120 discontinued before the randomized controlled trial (RCT) even began. So only 63% (205/325) could tolerate Opana at all, let alone achieve >50% pain relief. Furthermore, following the initial enriched enrollment phase, another 33% of the subjects randomized to Opana also failed to complete the trial due to adverse effects or lack of efficacy.³¹¹
- D. By ignoring the substantial percentage of patients who could not tolerate Opana at all (37%), and those who subsequently dropped out of the drug arm of the trial (33%), Endo trained its sales team to mislead physicians about its efficacy by making the false claim that “over 70%” achieved over 50% pain relief.
- E. Further, although the Katz article did not explicitly state that Opana can be used long-term for chronic pain, the training does not instruct the salesforce to limit use to 12 weeks.³¹² Also note that the Hale study,³¹³ to be used for

³⁰⁷ Katz M, Rauck R, Ahdieh H, *et al.* A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naïve patients with chronic low back pain. *Curr Med Res Opin.* 2007;23(1):117–128.

³⁰⁸ ENDO-CHI_LIT-00210473 at 0475

³⁰⁹ Katz, *et al.*, “12 Week Randomized Trial,” fn. 307, above, at p. 117.

³¹⁰ ENDO-CHI_LIT-00210473 at 0475

³¹¹ Katz, *et al.*, “12 Week Randomized Trial,” fn. 307, above, at p. 120.

³¹² ENDO-CHI_LIT-00210473 at 0474

the same sales calls, explicitly stated in the abstract that Opana provides “long-term analgesia,” despite a study length of only 12 weeks.³¹⁴ The claim of “long-term analgesia” is misleading in the context of a 12-week study.

- b. The impact of marketing material disseminated to prescribers under the guise of science cannot be overstated, especially in an era when practicing ‘evidence based medicine’ was and is the gold standard. The average busy clinician will never have time to wade through the voluminous literature, especially at the level of detail required to detect inaccuracies, and therefore relies on bottom line conclusions found in the abstract, trusting that a published peer reviewed article is a valid and reliable source.
- c. In their report “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,” The National Academies of Science, Engineering and Medicine stated, “... certain hypotheses about causes of the epidemic are inescapable ... *heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some)* and substantially increased prescribing by physicians were key contributors to the increase in misuse, OUD, and accompanying harms.”³¹⁵ (Emphasis added)
- d. According to the U.S. Drug Enforcement Administration, in a letter in the appendix of the 2003 GAO report cited previously, Purdue’s “aggressive methods, calculated fueling of demand Contributing to the abuse and diversion problem (and the product’s excessive availability) in promoting this drug to practitioners, Purdue deliberately minimized the abuse risk associated with OxyContin.... The claim in Purdue’s ‘educational’ video for physicians that opioid analgesics cause addiction in less than one percent of patients is not only unsubstantiated but also dangerous because it misleads prescribers.”³¹⁶ The DEA letter stated further, that Purdue’s distribution of branded promotional items such as fishing hats, stuffed animal plush toys and coffee mugs was “unprecedented for a Schedule II opioid”, and served as “an indicator of Purdue’s aggressive, excessive and inappropriate marketing of their product, OxyContin.”³¹⁷

³¹³ Hale ME, Ahdieh H, Ma T, Rauck R. Efficacy and Safety of OPANA ER (Oxymorphone Extended Release) for Relief of Moderate to Severe Chronic Low Back Pain in Opioid-Experienced Patients: A 12-Week, Randomized, Double-blind, Placebo-controlled Study. *J Pain*. 2007;8(2):175-184.

³¹⁴ *Id.* at p. 175.

³¹⁵ National Academies of Science Engineering and Medicine, “Pain Management and Opioid Epidemic 2017,” fn. 131, above, at pp. 40-41.

³¹⁶ Letter from Rogelio Guevara, Chief Inspector, DEA, to Marcia Crosse/GAO, 11/5/03; reprinted at GAO Report, “OxyContin Abuse,” fn. 56, above, at pp. 56-57.

³¹⁷ *Id.* at p. 56.

- e. As I wrote in my book, *Drug Dealer, M.D.*,³¹⁸ doctors were “duped” by the Pharmaceutical Opioid Industry into believing the myths of substantial benefits and very low risks of prescription opioids. I also wrote in my book that others had some responsibility for the events that have transpired. The roles of other parties are summarized below. In addition, on the basis of my review of documents that were provided to me in this case, I am more aware of the Pharmaceutical Opioid Industry’s role in influencing some of those other parties to act in the way they did.
- i. The Federation of State Medical Boards (FSMB) is a national organization that oversees the 70 medical and osteopathic boards of the United States and its territories. The State Board organizations serve many functions, but the most important is to police doctors, and exert disciplinary action against doctors who are deemed dangerous to patients. One of the most severe forms of disciplinary action is to revoke a doctor’s license to practice medicine.
 - A. In 1998, the Federation of State Medical Boards released a policy to reassure doctors that they would not be prosecuted if they prescribed even large amounts of opioids, as long as it was for the treatment of pain. Further, the Federation urged state medical boards to punish doctors for under-treating pain. Doctors lived in fear of disciplinary action from the State Medical Boards, and the lawsuit that usually followed, if they denied a patient opioid painkillers. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to adopt its Model Policy to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct.
 - B. In 2001, every licensed physician in the state of California was mandated to attend a day-long course on the treatment of pain, as a requirement to maintain licensure. I attended one of these courses, and to my recollection, all of the false messages promoted by the Defendants were highlighted in this CME course, including overstatement of benefits, and understatement of risks.
 - C. The Federation of State Medical Boards published a book promoting the use of opioid painkillers. This book was sponsored by a “consortium” that included Abbott

³¹⁸ Lembke, “*Drug Dealer, MD*,” fn. 2, above.

Laboratories, Alparma Pharmaceuticals, Cephalon, Inc., Endo Pharmaceuticals, the Wisconsin PPSG, and Purdue Pharma³¹⁹. (See Appendix II).

- D. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct. PPSG played a central role in revising the Federation of State Medical Board's Model Guidelines on the Use of Controlled Substances for Pain Management³²⁰, now entitled Model Policy for the Use of Controlled Substances for Pain Management.³²¹
- ii. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. They are responsible for approving drugs before they reach the market, and monitoring the safety and marketing of those drugs after they are publicly available. In my book, *Drug Dealer, MD*, I assigned some responsibility for the prescription drug epidemic to the FDA, and to the Defendants for efforts to influence the FDA. However, it is my understanding that other witnesses with expertise on FDA-related matters will offer testimony on such issues at trial, and, accordingly, I do not intend to testify on issues relating to the FDA.³²²
- iii. The Toyota-ization of Medicine
- A. The majority of doctors today work in large integrated health care systems. During the 1990's and 2000's, there occurred a mass migration of doctors out of private practice and into managed care organizations. In 2002, 70% of U.S. physician practices were physician-owned. By 2008, more than 50% of U.S. physician practices were owned and

³¹⁹ Fishman, S.(ed.), "Responsible Opioid Prescribing: A Physician's Guide" (Federation of State Medical Boards, Waterford Life Sciences, 2007).

³²⁰ WIS_PPSG_008292, 11/30/2005

³²¹

http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004_model_pain_policy.asp

³²² Lembke, "*Drug Dealer, MD*," fn. 2, above; Fauber J. FDA and Pharma: Emails Raise Pay-for-Play Concerns. *Sentinal/MedPage Today*. October 7, 2003, see <http://www.medpagetoday.com/PainManagement/PainManagement/42103>, at p. 1.

operated by hospitals or integrated health delivery systems, and that number just continues to rise.³²³

- B. The migration of doctors into integrated health care systems (hospital factories) has transformed medical treatment. Doctors work much less autonomously. Treatment options are often dictated by hospital administrators, (see Joint Commission) guidelines, and third-party payers (health insurance companies). The result is that doctors experience enormous pressure to get patients in and out quickly, to palliate pain, and to have ‘satisfied customers.’ This too has contributed to the problem of overprescribing.³²⁴
 - C. These structural factors opened the doors, but the aggressive marketing and misrepresentation of risks and benefits took advantage of these conditions to maximize sales and maximize harm.
 - D. I have also written, in “Drug Dealer, M.D.,” about the manipulative behaviors of patients in attempting to obtain opioid drugs from their doctors. These behaviors are not surprising; in fact they are diagnostic of the disease of addiction, whether the drug is OxyContin, or Opana, or heroin. In my opinion, the Pharmaceutical Opioid Industry has attempted to blame victims of the disease of addiction for the epidemic resulting from their own aggressive promotion of addictive drugs, while at the same time promoting the false message that patients taking these drugs for pain under a doctor’s prescription have little or no risk of addiction or overdose.
- f. Opioid prescribing in the United States far exceeds that of other developed nations with aging populations and comparable population needs for pain relief.
- i. Using International Narcotics Control Board figures, the United States consumed 173,332 kilograms of 574,693 kilograms of

³²³ Kocher R, Sahni N. Hospitals’ Race to Employ Physicians — The Logic Behind a Money Losing Proposition. *NEJM*. 2011;1790-1793, at p. 1791.

³²⁴ Lembke A. Why Doctors Prescribe Opioids to Known Opioid Abusers. *N Engl J Med*. 2012;367(17):1580-1581.

opioids consumed globally (382,131.6 of 1,266,981.2 pounds), or 30.2 percent.³²⁵

ii. Using “defined daily doses,” the United States consumed the most opioids per unit population from 2013 to 2015: 47,580 doses of narcotic drugs were consumed per day per million people. Canada comes in second with 34,444 defined doses consumed per million people per day, and Germany in third with 30,796; Japan was 50th at 1,223 defined doses/day.³²⁶

g. Attached to this Report is an Appendix of statements made by the Defendants in this litigation, which were contrary to medical and scientific evidence, or not sufficiently supported by the evidence to justify the enormous risks entailed by chronic opioid therapy. In broad terms, Defendants’ assertions overstated the benefits and understated the risks of chronic opioid therapy, as specified in but not limited to the representations listed in the Appendix.

11. The increase in opioid sales resulted in a prescription opioid epidemic in the United States. “Epidemic,” defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990’s and continuing to the present day. There is an undeniable link between suicide and opioids. This epidemic is first and foremost a prescription opioid epidemic, with prescription opioids accounting for a higher number of cumulative deaths to date (1999-2017) than heroin and illicit fentanyl combined.

a. Based on CDC data, between 1999 and 2017, 230,869 people died from opioid pain relievers (excluding non-methadone synthetics, predominantly fentanyl). In the same time period, 100,599 died from heroin, and 93,151 people died from non-methadone synthetics (predominantly fentanyl), for a total of 193,750 deaths due to heroin and illicit fentanyl. Although these numbers are staggering, the cumulative death toll from opioid pain relievers (230,869) is more than that of heroin and illicit fentanyl combined (193,750).³²⁷ In short, while there has been an obvious recent spike in deaths related to heroin and illicit fentanyl, the number of deaths caused by non-fentanyl prescription opioids remains unacceptably high, and cumulatively exceeds deaths associated with heroin and fentanyl.

Prescription opioid related deaths, excluding fentanyl and methadone, did not decline from 2016 to 2017, the last year for which CDC data are available, but in fact remained essentially identical (14,487 deaths in 2016;

³²⁵ International Narcotics Control Board, *Narcotic Drugs Technical Report 2016*, at pp. 200-203. See https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2016/narcotic-drugs-technical-report-2016.html.

³²⁶ *Id.* at pp. 226-228.

³²⁷ Centers for Disease Control and Prevention, *Data Brief 329. Drug Overdose Deaths in the United States, 1999–2017*. https://www.cdc.gov/nchs/data/databriefs/db329_tables-508.pdf#page=1, at p. 4.

14,495 deaths in 2017).³²⁸ A report just released by the CDC shows that drug overdose deaths in women aged 30–64 years due to prescription opioids have been steadily rising between 1999 and 2017. “The crude rate for deaths involving prescription opioids increased from 1999 to 2017 for every age group, with the largest increases (>1,000%) among women aged 55–64 years.”³²⁹

- b. An article published in *Science* in 2018 by Jalal, et al, “Changing Dynamics of the Drug Overdose Epidemic in the United States from 1979–2016,”³³⁰ suggests that mortality data from numerous “drug-specific subepidemics” can be fitted to a smooth exponential curve during that time period. However, the authors note the “paradox” presented by these results, since the data combine mortality associated with subepidemics as disparate as heroin and fentanyl deaths in the northeastern United States with methamphetamines in the southwestern states.³³¹ Accordingly, an after-the-fact fitting of 38 years of combined data to a smooth curve does not obviate the need to understand each subepidemic on its own terms. In the case of prescription opioids, factors relevant to that epidemic have been addressed throughout this report, and are summarized as follows:
 - i. The sheer scale of access to opioids made possible through opioid overprescribing during this time period, led individuals who otherwise would never have been exposed, to use and subsequently be killed by opioids.
 - ii. The lethality of opioids sets opioids apart from other drugs. Indeed the apparent continuity of the overdose mortality rate curve in the Jalal *et al.* article, on closer inspection, shows a definitive rise above the smooth curve between 2001 and 2010, corresponding to the prescription opioid epidemic.³³²
 - iii. An efficient distributor supply chain made prescriptions opioids available on a mass scale to large numbers of people in rural and remote settings, expanding both the licit and illicit drug market, and sets this opioid epidemic apart from prior epidemics and other drug epidemics.

³²⁸ *Id.* at p. 4.

³²⁹ VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(1):1–5, at p. 2.

³³⁰ Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science* (80-). 2018. doi:10.1126/science.aau1184.

³³¹ *Id.* at p. 1.

³³² *Id.*

- iv. The problem of addiction more broadly in society and culture today does not negate the significant role of opioids manufacturers and distributors in causing this epidemic.
- v. Although forces may be operative to accelerate demand, such as despair, loss of purpose, and dissolution of communities, studies show that the ‘push’ of increased access to opioids has played a bigger role than the ‘pull’ of despair.³³³
- c. Opioid deaths are only one measure of this epidemic
 - i. 11 million people misused prescription opioids in 2016, compared to the approximately 1 million people using heroin. In 2011, according to a CDC report, 11 million people reported nonmedical use of opioid analgesics. “Moreover, chronic nonmedical use of opioid analgesics (i.e. nonmedical use on 200 days or more in the past year) increased roughly 75% between 2002-2003 and 2009-2010 .This increase means that on average in 2009-2010 there were nearly 1 million people in the U.S. with chronic nonmedical use of opioid analgesics.”³³⁴
 - ii. Nearly 2 million (0.8%) of people in the United States are addicted to opioids based on estimates from the 2015 National Survey on Drug use and Health (NSDUH).³³⁵
 - iii. According to the CDC, among approximately 45 million emergency department visits reported by the 16 Enhanced State Opioid Overdose Surveillance (ESOOS) states from July 2016 through September 2017, “a total of 119,198 (26.7 per 10,000 visits) were suspected opioid overdoses. Opioid overdose ED visits increased 34.5% from third quarter 2016 to third quarter 2017 Ten states experienced significant increases in prevalence during this period, although substantial variation was observed among states in the same region. All states in the Midwest reported significant increases, including Wisconsin (108.6%), Illinois

³³³ Ruhm CJ. Deaths of Despair or Drug Problems? NBER Working Paper No. 24188, NBER Program(s):Health Care, Health Economics, Public Economics (2017).

³³⁴ United States Department of Health and Human Services. Addressing Prescription Drug Abuse in the United States. :1-36, at pp., 9-10. See https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf

³³⁵ Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Annals of internal medicine*. 2017;167(5):293-301. Epub 2017/08/02. doi: 10.7326/m17-0865. PubMed PMID: 28761945, at p. 293.

(65.5%), Indiana (35.1%), Ohio (27.7%), and Missouri (21.4%).”³³⁶

- iv. Unlike the available fatal overdose data, which are categorized according to non-fentanyl prescription opioids, heroin, etc., the CDC/ESOOS on emergency department visits are not broken out into categories. Although the cumulative total of prescription opioid mortality since 1999 exceeds mortality for fentanyl plus heroin, the mortality rate for the latter category has recently begun to exceed the former; it is likely that the nonfatal overdose hospital admissions have occurred in a similar ratio of prescription opioids to illicit heroin and fentanyl.
- v. As described previously, tens of thousands of Americans experience non-fatal overdose, both in medical settings, like the emergency department, and in the field, creating a significant burden on the health care system and on first responders, not to mention the victims of near overdose themselves. In a paper by Dunn et al.,³³⁷ previously discussed, the over 14,000 fatal prescription opioid overdoses in 2017³³⁸ would translate to over 100,000 nonfatal overdoses during that same year. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, to treat the overdose episode itself, and to provide long-term care for the OUD disease that gave rise to the event.

12. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). There is a clear link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids. The likelihood of heroin addiction is 40 times greater in those who have previously misused or been addicted to prescription opioids, and fentanyl, in turn, has contaminated the heroin supply.

- a. “A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a gateway to increased heroin use³³⁹ ... The interrelated nature of the

³³⁶ Vivolo-Kantor AM, Seth P, Gladden RM, Mattson CL, Baldwin GT. Vital Signs : Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States , July 2016 – September 2017. 2018;67(9):279-285, at p. 281.

³³⁷ Dunn, *et al.*, “Opioid Prescriptions,” fn. 268, above.

³³⁸ CDC, Data Brief 329, fn 327, above, at p. 4.

³³⁹ National Academies of Science Engineering and Medicine (NASEM), “Pain Management and Opioid Epidemic 2017,” fn. 133, above, at p. 215.

prescription and illicit opioid epidemics means that one cannot be addressed separately from the other.”³⁴⁰

- b. In the 1960s, 80% of opioid users reported that their first exposure to opioids was in the form of heroin. In the 2000s, 75% of opioid users reported that their first exposure to opioids was in the form of prescription painkillers.³⁴¹
- c. The incidence of heroin use among people who reported prior nonmedical use of prescription opioids was 19 times as high as the incidence among persons who reported no previous nonmedical use.³⁴²
- d. Prescription opioid use disorder/addiction is associated with a likelihood of heroin addiction that is 40 times as great as the likelihood with no prescription-opioid misuse or addiction, even after accounting for sociodemographic, geographic, and other substance abuse or dependence characteristics.³⁴³
- e. Eighty-six percent of urban people who used injected heroin in New York and Los Angeles in 2008 and 2009 had used opioids nonmedically before using heroin.³⁴⁴ Similar studies conducted in San Diego, Seattle, and New York showed that 40%, 39%, and 70% of heroin users, respectively, reported that they had used prescription opioids nonmedically before initiating heroin use.³⁴⁵
- f. Muhuri found that 79.5% of persons who recently began using heroin had used prescription opioids nonmedically before initiating heroin use.³⁴⁶
- g. The number of Americans aged 12 and older with past month heroin use, rose from 281,000 to 335,000 between 2011 and 2013, a significant increase from the 166,000 using heroin in 2002.³⁴⁷
- h. Deaths due to illicit fentanyl have also been on the rise. Fentanyl is 50-100 times as potent as heroin, and when mixed in with heroin or other illicit

³⁴⁰ *Id.* at p. 248.

³⁴¹ Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the united states: A retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014. doi:10.1001/jamapsychiatry.2014.366, at p. E-1.

³⁴² Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the united States. *CBHSQ Data Rev*. 2013;(August):1-16, at p. 1.

³⁴³ Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med*. 2016. doi:10.1056/NEJMr1508490, at p. 157.

³⁴⁴ Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy*. 2012;23(1):37-44, at p. 41.

³⁴⁵ Compton, *et al.*, “Relationship Between Opioid and Heroin Use,” fn. 343, above, at p. 156.

³⁴⁶ Muhuri, *et al.*, “Associations of NMPR and Heroin,” fn. 342, above, at p. 1.

³⁴⁷ McCarthy M. Illicit drug use in the US holds steady, but heroin use is on rise. *BMJ*. 2013;347(September):f5544. doi:10.1136/bmj.f5544, at p. 1.

drugs without the users' knowledge, an unsuspecting user is more vulnerable to overdose.

- i. In my opinion, the epidemic of prescription opioid use beginning in the 1990s has been a significant factor contributing to the subsequent increase in heroin and fentanyl use. As the data show, the use of addictive prescription opioids commonly precedes the use of addictive heroin and fentanyl.

13. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to be exposed and become addicted, including individuals who turned from prescription opioids to illicit sources of opioids such as heroin (The Gateway Effect).

- a. The Purdue "Project Tango" Power Point presentation, referenced above, includes the following quote on the slide that shows the definition of addiction along with the statistical data on the numbers and growth rate of addiction: "'This can happen to any-one—from a 50 year old woman with chronic lower back pain to a 18 year old boy with a sports injury, from the very wealthy to the very poor.' Pain specialist Cornell Weill, 100 patients/week."³⁴⁸ I agree with this statement, and it is relevant to "The Gateway Effect," whereby the trajectory to addiction begins with exposure to prescription opioids. (Note: a statement like this never made an appearance in Purdue material, internal or external, when they were marketing opioids for pain, but is now front and center as they pursue the addiction treatment market. Indeed when it came to marketing opioids for pain, Purdue and other Defendants pushed the idea that only a few vulnerable "addicts" could get addicted, and that the vast majority of patients were somehow immune.)
- b. Teens are especially vulnerable to the increased access to prescription drugs. Adolescence is a time when the rapidly growing brain is more plastic, and therefore more vulnerable on a neurological level, to potentially irreversible brain changes caused by chronic drug exposure.³⁴⁹ Teens are also more likely to take risks, without appreciating the adverse consequences associated with those risks.
- c. As mentioned above, opioids are generally considered appropriate for cancer pain. However, patients with cancer related pain, even at the end of life, are not immune to addiction and they should be monitored carefully for addiction and other adverse consequences, and should receive the lowest dose for the shortest possible duration.

³⁴⁸ PPLPC016000255303, produced natively at *9.

³⁴⁹ HHS, "Addressing Prescription Drug Abuse," fn. 334, above, at p. 189.

- i. A first person perspective piece in the New England Journal of Medicine, describes the experience of an oncologist (cancer doctor) whose patient gets addicted to opioids.³⁵⁰ In my clinical experience, opioid misuse and addiction are as common among cancer patients as non-cancer patients.
- ii. There were more than 15 million cancer survivors in the United States in 2016.³⁵¹ Even patients with cancers once considered incurable, now go into remission for decades and more, emphasizing the need for caution in treating a very large population of patients with opioids.

14. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to become dependent on opioids (independent of addiction), and suffer significant morbidity and mortality as a result (The Dependence Effect).

- a. Over the last 30 years, the liberal prescribing of opioids for chronic pain has created a “legacy” population of patients who have been on opioids for several years if not decades, and are now physically dependent on opioids, making it difficult to come off. There are no exact numbers on how many Americans are opioid dependent. In a Washington Post Kaiser Family Foundation survey of patients receiving opioids for pain, 34% report becoming physiologically dependent on prescription opioids.³⁵²
- b. By 2005, long-term opioid therapy was being prescribed to approximately 10 million Americans. “In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. Of these prescriptions, 65% were for short-term therapy (<3 weeks), but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.”³⁵³
- c. According to a 2019 study, prescribing of opioids has declined from its peak but still vastly exceeds the level of prescribing before the epidemic began in the 1990s, and prescription length continues to increase. Opioid prescriptions per person in the total US increased annually at an average rate of 6.9% per year until 2010, and decreased at an average rate of 3.8% per year from 2010 through 2015. In Ohio, MME per person increased by an average of 6.1% per year from 2006 through 2010; decreased on

³⁵⁰ Loren AW. Harder to Treat Than Leukemia - Opioid Use Disorder in Survivors of Cancer. *NEJM*. 2018;379(26).

³⁵¹ Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the “silver tsunami”: Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016. doi:10.1158/1055-9965.EPI-16-0133, at p. 1029.

³⁵² Users P-K survey of long-term prescription opioid painkiller. Washington Post Kaiser Long-Term Prescription Opioid Painkiller Users Poll, Oct. 3-Nov. 9, 2016, at p. 10.

³⁵³ Volkow, *et al.*, “Misconceptions and Mitigation,” fn. 16, above, at p. 1253.

average by 6.7% per year from 2010 through 2015, and decreased 12.7% per year from 2015 through 2017. However, prescription duration increased in Ohio from 12.4 days in 2006 to 19.3 days in 2017.³⁵⁴ Duration of exposure is a major risk factor for OUD.

- d. A newborn is born dependent on opioids as a result of being exposed to opioids in utero. According to DSM-5 criteria, the opioid dependent newborn is not ‘addicted,’ because addiction requires the manifestations of certain pathological and maladaptive behaviors in conjunction with opioid use. The newborn is the passive recipient of opioids due to the mother’s exposure.
 - i. The rate of admission to NICU [neonatal intensive care units] for neonatal abstinence syndrome (NAS), a drug-withdrawal syndrome that occurs after in utero exposure to opioids, increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions between 2004 and 2013.³⁵⁵
 - ii. Tolia reported that “the median length of stay increased from 13 days to 19 days ($P < 0.001$ for both trends). The total percentage of NICU [neonatal intensive care unit] days nationwide that were attributed to the neonatal abstinence syndrome increased from 0.6% to 4.0% ($P < 0.001$ for trend), with eight centers reporting that more than 20% of all NICU days were attributed to the care of these infants in 2013.”³⁵⁶
 - iii. This approximate quadrupling of the rate of NAS is directly attributable to the epidemic of opioid use disorder that began with promotion of prescription opioids and continues to the present, accompanied by use of illicit opioid drugs.

15. The increased sales of prescription opioids harmed communities by causing a dramatic increase in the widespread availability of opioids, including to persons for whom opioids had not been prescribed (The Tsunami Effect). Medical prescriptions are the primary conduit for prescription opioid misuse. Less than 10% of Americans misusing prescription opioids got them from a “street dealer.”

- a. It’s important to recognize that although many of the communities hit hardest by the opioid epidemic were already struggling with serious social and economic problems, the sudden availability of and easy access to

³⁵⁴ Schieber, L, Guy, G, *et al.*, Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017, at pp. 4-5.

³⁵⁵ Tolia VN, Patrick SW, Bennett MM, *et al.* Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *Obstet Gynecol Surv.* 2015. doi:10.1097/OGX.000000000000243, at p. 2118.

³⁵⁶ *Id.* at p. 2118.

opioids, initially in prescription pill form, contributed to the economic and social devastation of many towns across America.³⁵⁷

- b. Economic downturn and the efflux of manufacturing jobs in towns across America in the last thirty years, have contributed to so-called “deaths of despair” – early mortality in middle aged non-Hispanic whites due primarily to drug overdose.³⁵⁸ Nonetheless, economic disadvantage contributes only 10-20% of mortality risk attributable to opioids, whereas the larger share of risk is due to supply of opioids in a given geographic region.³⁵⁹
- c. The opioid epidemic is partly responsible for the spread of Hepatitis C, HIV and other infectious diseases across the country in recent years, as people who become addicted to prescription opioids, transition to injection drug use and share needles with others who are infected. For example, the outbreak of Hep C and HIV in Scott County, Indiana in 2015, “resulted from inappropriate prescribing of opioid medications.”³⁶⁰

16. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

- a. Primary prevention: Preventing new cases of the disease by limiting access to opioids, re-educating prescribers, and rebuilding communities devastated by the epidemic.
 - i. Opioids should not be prescribed as first line treatment for most forms of pain. Exceptions include cases of severe tissue injury, peri-operatively when multimodal analgesia is insufficient, and as palliative/end of life care.
 - A. For acute pain, the CDC guidelines recommend no more than 3 to 7 days of opioid treatment. Even within this general guideline, it is important to limit both the dose and frequency of administration of opioid drugs during the 3-7 day window, to minimize the increase in long-term use that

³⁵⁷ Ruhm, *et al.*, “Deaths of Despair,” fn. 333, above.

³⁵⁸ Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci.* 2015. doi:10.1073/pnas.1518393112, at p. 15081.

³⁵⁹ Ruhm, *et al.*, “Deaths of Despair,” fn. 333, above.

³⁶⁰ Strathdee SA, Beyrer C. Threading the Needle — How to Stop the HIV Outbreak in Rural Indiana. *N Engl J Med.* 2015. doi:10.1056/NEJMp1507252, at p. 398.

has been documented following higher doses of opioids for acute pain.³⁶¹

- B. First line treatment for pain should include non-opioid medications and non-medication treatment for pain (non-opioid medications, physical therapy, psychotherapy). The latter are especially important for the treatment of chronic pain.
 - C. There may be unusual instances when opioid medications can be used to good effect in the treatment of chronic pain; but even in this setting, avoiding daily use to avoid tolerance and dependence is recommended. Further, very close monitoring for the emergence of adverse medical consequences, including misuse and addiction, using objective criteria such as urine toxicology and database scrutiny, are essential components of a safe and effective treatment plan. Further, an exit strategy for cessation of opioid therapy is necessary, should risks outweigh benefits at any point in the treatment, in recognition that most patients will have become dependent and will taper with difficulty.³⁶²
- ii. Data on the impact of interventions to curb opioid prescribing have recently become available supporting the view that limiting opioid prescribing in a systematic way reduces prescription opioid-related overdose deaths without adversely compromising pain treatment.
- A. Massachusetts had the first of its kind state-wide acute care prescribing limits and a required-check of the Prescription Drug Monitoring Programs (PDMPs) prior to opioid prescribing. As a result they reduced opioid prescriptions by 30%.³⁶³
 - B. The Department of Public Health determines mean and median quantity and volume of prescriptions for opioids, within categories of similar specialty or practice types. Prescribers who exceed mean or median will be sent notice.³⁶⁴

³⁶¹ Delgado, *et al.*, “National Variation,” fn. 288, above, at p. 389.

³⁶² Dunn, *et al.*, “Opioid Prescriptions,” fn. 268, above, at p. 86.

³⁶³ Massachusetts Department of Public Health Press Release, “Year Over Year Opioid-Related Overdose Deaths Decline in Massachusetts; Opioid Prescriptions Fall 30 Percent”, August 24, 2018. See <https://www.mass.gov/news/year-over-year-opioid-related-overdose-deaths-decline-in-massachusetts-opioid-prescriptions>.

³⁶⁴ *Id.*

- C. The law establishes a drug stewardship program to be paid for by drug companies that makes it easier for patients to safely dispose of unwanted and unused medications. Effective Jan. 1, 2017.³⁶⁵
- D. The State has launched core competencies for safe prescribing of opioids in the state’s medical schools, community health centers, nursing, physician assistant, dental schools and schools of social work.” (emphasis in original) Commensurate with decreases in opioid prescribing, Massachusetts has seen a decrease in opioid-related overdose deaths: “Opioid-related overdose deaths in Massachusetts have fallen steadily over the past three quarters even as the presence of fentanyl in overdose deaths reached an all-time high... Overall in 2017 there was a 4 percent decrease in opioid-related overdose deaths from 2016. The data also shows that the Commonwealth has experienced a 30 percent decline in opioid prescriptions since the launch of the Massachusetts Prescription Monitoring Program (MassPAT) in August 2016.”³⁶⁶
- E. A successful program in Chittenden County, Vermont achieved a 50% decline in opioid mortality through a multi-faceted program that included an increased capacity “hub” (the County) and increased number of physicians treating opioid addiction (the “spokes”); a Safe Recovery syringe exchange center and low-barrier sites for buprenorphine treatment; and support for a recent statute requiring such medications to be provided to prisoners with addiction treatment.³⁶⁷
- iii. As noted in the *New England Journal of Medicine* in 2010, prescription opioids are “essentially legal heroin.” In a comment as to how the FDA should revise a Risk Evaluation and Management Strategy (REMS) for use of opioids, a FDA Advisory Board member stated, “We need to think about how we would construct a REMS if we were going to be marketing heroin.”³⁶⁸ I agree with these statements, since prescription opioids are as addictive as heroin and operate on the same neuro-circuitry in the same

³⁶⁵ *Id.*

³⁶⁶ *Id.*

³⁶⁷ City of Burlington, Mayor’s Office, Press Release, “Mayor Miro Weinberger and Community Partners Announce 50 Percent Decline in Opioid-Related Overdose Fatalities in Chittenden County in 2018 (February 14, 2019). See <https://www.burlingtonvt.gov/Press/mayor-miro-weinberger-and-community-partners-announce-50-percent-decline-in-opioid-related>.

³⁶⁸ Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med.* 2010;363(21):1981-1985. doi:10.1056/NEJMp1011512, at p. 1981.

manner. Current REMS training is insufficient to educate prescribers about the risks of opioids. We need more comprehensive prescriber training on the evidence of benefits and harms with opioids for medical use, how to monitor patients taking opioids for medical use, how to taper patients off opioids, and how to intervene when a problem arises.

- iv. Medical and nursing schools across the country are beginning to implement addiction medicine curricula, an essential part of the reform process to combat this epidemic. I have led an initiative here at Stanford University School of Medicine to create our first ever addiction medicine curriculum since 2017, and I am involved in promoting similar initiatives across the country.
 - A. I testified at a White House symposium³⁶⁹ on the importance of educating health care providers on addiction treatment and safe prescribing. At that symposium, I suggested a school loan repayment program to incentivize health care providers to treat addiction in underserved areas after completing their training. This suggestion was taken up by Representative Clark and Representative Rogers as the Substance Use Disorder Workforce Loan Repayment Bill, which was included as a key provision in the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act, also known as the SUPPORT Act, passed September 28, 2018. Although the legislation was approved, there is yet to be a source of funding.
 - B. I am the Program Director for Stanford's Addiction Medicine Fellowship, a one-year fellowship to provide advanced training in addiction medicine. I also work on a national level to promote these fellowships, and was the inaugural president of the Addiction Medicine Fellowship Directors' Association (AMFDA).
 - C. I have authored articles on the importance of teaching addiction medicine to medical students, residents, and fellows, including "The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine" (*Academic Psychiatry*, 2018)³⁷⁰ and "Qualitative

³⁶⁹ The Addiction Medicine Foundation, "Congressional Briefing – Addiction Medicine: The Urgent Need for Trained Physicians" (September 28, 2017), see <https://www.youtube.com/watch?v=y6kBoQckmHw>

³⁷⁰ Lembke A, Humphreys K. The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine. *Acad Psychiatry*. 2018;42(2):269-272. doi:10.1007/s40596-018-0892-8.

Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum (Academic Psychiatry 2018).³⁷¹ In these articles, I address the need for more robust training in the screening and intervention of patients with the full spectrum of opioid use disorders (including misuse and dependence). I further recommend increasing medical school hours of training in addiction medicine, including safe prescribing of controlled substances.

- v. Consider prohibiting the pharmaceutical industry from funding or influencing Continuing Medical Education (CME) courses for prescribers.
 - vi. Consider promoting CME education which explicitly eschews industry funds and influence, and providing academic detailing (unbiased, evidence based information for prescribers).
 - vii. Earmark money to provide medical school, residency, and fellowship training in addiction treatment.
- b. Secondary prevention: limit progression of harm by helping patients on dangerously high doses come down or off of opioids, independent of whether they are addicted, and by implementing harm reduction strategies to mitigate the dangers of opioids.
- i. To accomplish effective, safe, and compassionate opioid tapers in this country, we need funding to build de-prescribing clinics to provide treatment for opioid dependent patients. Where de-prescribing clinics are not feasible, we need to embed an interdisciplinary, chronic care treatment team inside of primary care to support deprescribing/opioid tapering. This chronic care team would consist of physicians, nurses, social workers, case workers, psychologists, and others trained to help patients manage the physically and emotionally taxing process of decreasing prescribed opioids. Primary care doctors, already overloaded with responsibilities, are unlikely to achieve successful tapers in opioid dependent, high dose legacy patients, without significant incentives and support. This will require an enormous investment of resources, as it is estimated that millions of Americans are dependent on opioids and suffering from or at heightened risk for adverse consequences.

³⁷¹ Raber I, Ball A, Papac J, Lembke A, *et al.* Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum. *Acad Psychiatry*. 2018;42(5):664-667.

- ii. I worked with colleagues at Stanford to develop a protocol for helping opioid dependent patients compassionately and safely taper down or off of prescribed opioids: “The BRAVO Protocol.” The protocol has been adopted by the Oregon Pain Guidance, the Oregon Pain Task Force, and has influenced other opioid task forces around the country who are struggling with the problem of opioid dependent (but not addicted) chronic pain patients.³⁷²
- iii. We have created a free online continuing medical education course - “The BRAVO Protocol: How to Taper Patients Off of Chronic Opioid Therapy.” This course, created in conjunction with the Stanford continuing medical education office, teaches prescribers how to safely and compassionately taper opioids, something that is not currently taught in medical schools.
- iv. The course has been positively featured in the lay press, highlighting that the course features the first-person account of a patient who was, with support, able to taper off of opioids and experienced improved chronic pain as a result.³⁷³ We have created a companion page summarizing The BRAVO Protocol, which has gained wide informal distribution among prescribers. It summarizes the key learning points as below. (See BRAVO Protocol summary attached to this report.) The bottom line is, helping patients to decrease or discontinue long term opioid therapy presents a challenging clinical scenario, especially in patients on high doses (greater than 80 MEDs), with moderate to severe chronic pain, and co-occurring mental health disorders (depression, anxiety, PTSD). For this type of complex chronic pain patient, the usual recommendation to decrease opioids by 10% of the starting dose every week frequently will not apply. These patients often need slower tapers on the order of 5-10% decreases or less every month. Expert consensus suggests the taper speed should be tailored to the individual needs of the patient. Some patients who have been on opioids for years to decades, may require *years* to taper their dose. With this complex chronic pain patient in mind, the BRAVO protocol outlines a safe and compassionate strategy to approach opioid tapering, while also maintaining a therapeutic alliance between the treatment team and each patient.

³⁷² Oregon Health Authority Oregon Opioid Taper Guidelines Task Force Resources. See <https://www.oregon.gov/oha/PH/PreventionWellness/SubstanceUse/Opioids/Documents/taskforce/tapering-taskforce/2019-Opioid-Taper-Task-Force-Resources.pdf>.

³⁷³ Parloff R. Tapering off long-term Rx opioids: a first-hand account, Opioid Institute. (October 15, 2018) See <https://opioidinstitute.org/2018/10/15/tapering-opioids-lembke/>.

- v. Other harm reduction strategies include increasing naloxone distribution, promoting clean needle exchanges, improving patient education regarding safe medication storage and appropriate disposal of excess medications, and increasing public awareness of poison center services.

- c. Treatment

- i. We need a robust infrastructure to treat addiction, inside and outside of medicine. Such an infrastructure does not currently exist. Instead what we have are siloes of care with limited and contingent funding, or treatment centers accessible only by the rich.
- ii. Addiction treatment should be offered within every hospital, clinic, emergency room, jail, drug court, etc., across America. ‘Meeting patients where they are’ has become a mantra for the field. Patients with this complex behavioral illness are more likely to engage in treatment when they are offered treatment in settings where they are frequently found, like in hospitals, emergency rooms, jails, and even in settings where they might be using drugs (such as at the site of first responders, clean needle exchange sites, safe consumption sites, etc.).
- iii. An effective addiction treatment infrastructure should be based on evidence-based treatments for addiction, including buprenorphine, methadone maintenance, and naltrexone. Opioid agonist therapy (buprenorphine or methadone maintenance) has one of the most robust evidence bases of any addiction treatment. Multiple placebo controlled trials over many decades have demonstrated the efficacy of opioid agonist therapy in the treatment of opioid use disorder.³⁷⁴
- iv. Addiction is a chronic relapsing and remitting disorder, requiring a chronic care model and a team based approach, including a peer recovery coach, care coordinator, behavioral health specialist, licensed counselor, and a primary care professional.³⁷⁵ One way to address this problem within our current health care system, is to co-locate behavioral health specialists within primary care, or create a hub and spoke model with specialty clinics providing support to primary care clinics. A concurrent strategy is to build Centers of Excellence for Addiction Treatment at every major

³⁷⁴ Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: evidence for effective interventions. *Lancet*. 2012;379(9810):71-83, at p. 78.

³⁷⁵ “The Addiction Recovery Medical Home As An Alternative Payment Model,” Health Affairs Blog, December 12, 2018. DOI: 10.1377/hblog20181211.111071. *Heal Aff Blog*. doi: 10.1377/hblog20181211.111071, at p. 3.

medical center around the country, similar to existing Centers of Excellence for cancer, cardiac disease, and diabetes.

- v. As a chronic illness, addiction can require lifelong treatment. In my clinical experience, most people with moderate to severe opioid use disorder struggle to some degree to remain abstinent for the rest of their lives and there is a high rate of relapse when individuals go off of MAT treatment. Thus, the abatement plan to address the opioid epidemic should focus on providing the maximum level of both MAT and non-MAT treatment resources possible, as quickly as possible, and should maintain this level of treatment through at least 2034, as contemplated in the proposed abatement plan.
- vi. A successful treatment system would allow for those with the disease to titrate their treatment based on illness severity over time, with the recognition that the normal course of addiction involves periods of remission and recurrence, just like cancer.
- vii. Addiction treatment and recovery requires intensive individual and/or group therapy interventions, which should be integrated into treatment alongside medications.
- viii. Mutual help groups such as Narcotics Anonymous have a long tradition of aiding people with addiction achieve and maintain recovery. New models employing peer counselors as part of an interdisciplinary medical team to treat and target addiction, are being investigated. These models should be considered as a way to bridge inpatient and outpatient treatment and sustain recovery as patients return to their normal lives. Undergirding the creation of a robust infrastructure to target and treat addiction, is the need for a trained workforce to deliver this care. In Ohio, Office-Based Opioid Treatment on buprenorphine products has steadily increased, from 12,089 patients in 2008, to 67,665 in 2017.³⁷⁶

17. With an aggressive infusion of resources and efforts in Summit and Cuyahoga counties, it would be reasonable that within four years the number of bellwether individuals with OUD who receive substance abuse treatment services within a year could double, assuming that only 20% of individuals with OUD currently receive treatment. Note: 20% estimate based on SAMHSA: “Only 20% with OUD received specialty addiction treatment”³⁷⁷

³⁷⁶ Rick Massatti, Treatment Options for Opioid Use Disorder in Ohio. Ohio Mental Health and Addiction Services. 28th September 2018. Presented. At slide 8.

³⁷⁷ Substance Abuse and Mental Health Service Administration, “SAMHSA/HHS: An Update on the Opioid Crisis”, March 14, 2018, at p. 2. See https://www.samhsa.gov/sites/default/files/aatod_2018_final.pdf

18. With an aggressive infusion of resources and efforts in these two counties, it would be reasonable that within four years the percentage of bellwether individuals with OUD who receive MAT could quadruple from approximately 7% of individuals with OUD currently to approximately 28% of individuals with OUD. Note: 7% estimate based on assumption that 1/3 of individuals receiving treatment also receive MAT. Corresponds to national figures that less than 10% with OUD receive MAT.³⁷⁸

- a. Once the populations receiving treatment/MAT are increased as described above, it would be necessary to provide treatment at those same levels for the foreseeable life expectancy of the patients, because OUD is a disease with constant risk and high rate of relapse and remission.
- b. If the treatment rates described above are achieved, there would be a large impact on deaths and other outcomes, as evidenced by the experience in Massachusetts and Vermont, described above. The mix of MAT that is buprenorphine and naltrexone-based will continue to increase relative to methadone-based

D. Conclusion:

The ongoing epidemic of morbidity and mortality due to prescription opioids is the result of aggressive marketing and promotion of such drugs, and in particular the overstatement of benefits and understatement of harms. Opioid manufacturers engineered the increase in opioid prescribing by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like *The Joint Commission*, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread use.

Authoritative reviews have concluded that the evidence of benefits for chronic pain is “weak,” “inconclusive,” and “insufficient to assess effects on health outcomes.” Defendants’ clinical trials were too short to provide reliable evidence of long-term benefit, especially in light of highly selected populations and substantial rates of attrition from the studies. As shown by the SPACE trial, a gold standard, long-term study by independent researchers, non-opioids are as good or better than opioids for chronic pain, and have fewer side effects. On the risk side, Defendants claimed that addiction was “rare,” “uncommon,” or “less than 1%,” based on inapplicable data from non-comparable populations. The true rate of addiction in a clinical population is probably closer to 21-29%, across the full spectrum of OUD. In addition, there are millions of patients today who are physiologically dependent on opioids, unable to reduce their doses, and left to suffer the risks and consequences of long-term opioid therapy.

Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the

³⁷⁸ Sandoe, E., *et al.*, “Policy Levers That States Can Use to Improve Opioid Addiction Treatment And Address the Opioid Epidemic”, Health Affairs Blog. (Oct. 2, 2018). See <https://www.healthaffairs.org/doi/10.1377/hblog20180927.51221/full/>

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following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). In a *New England Journal of Medicine* commentary regarding the CDC Opioid-Prescribing Guideline, CDC physicians Thomas Frieden and Debra Houry stated, “We know of no other medication routinely used for a nonfatal condition that kills patients so frequently.”³⁷⁹

Dated: March 25, 2019

A handwritten signature in black ink, appearing to read 'Anna Lembke', written over a horizontal line.

Anna Lembke, M.D.

³⁷⁹ Frieden TR, Houry D. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med*. 2016. doi:10.1056/nejmp1515917, at p. 1503.